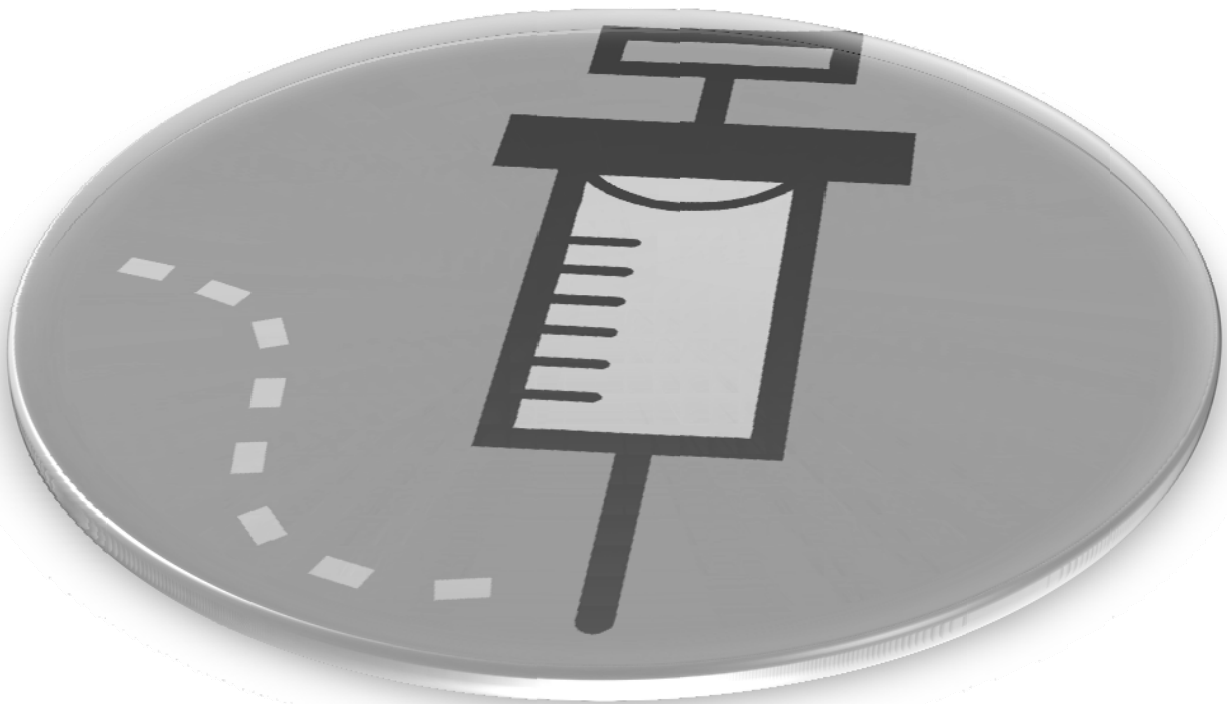


ANESTHETIC PHARMACOLOGY



INCLUDES

- ▶ **CHAPTER 1:** Mechanism of action of general anesthetics.
Intravenous anesthetics.
- ▶ **CHAPTER 2:** Inhalational anesthetics.
- ▶ **CHAPTER 3:** Neuromuscular blocking agents.
- ▶ **CHAPTER 4:** Analgesics.
- ▶ **CHAPTER 5:** Local anesthetics.
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Be aware: All information written in ITALIC form and in this FONT (Century gothic font) is for your basic knowledge only.

ABBREVIATIONS:

- ✚ **5-HT:** 5-Hydroxy Tryptamine (Serotonin).
- ✚ **↑ or ++:** Increases, Facilitates, or Stimulates.
- ✚ **↓ or --:** Decreases, Depresses, or Inhibits.
- ✚ **Δ:** Pyramidal tract.
- ✚ **ABP:** Arterial Blood Pressure.
- ✚ **Ach:** Acetylcholine.
- ✚ **BBB:** Blood Brain Barrier.
- ✚ **βB:** Beta-Blockers.
- ✚ **BP:** Blood Pressure.
- ✚ **BV:** Blood Vessels.
- ✚ **CIC:** Cardiac Inhibitory Center.
- ✚ **CNS:** Central Nervous System.
- ✚ **COP:** Cardiac Out Put.
- ✚ **CTZ:** Chemical Trigger Zone.
- ✚ **CVS:** Cardio-Vascular System.
- ✚ **ECT:** Electro-Convulsive Therapy.
- ✚ **EEG:** Electro-Encephalo-Gram.
- ✚ **FB:** Foreign Body.
- ✚ **GFR:** Glomerular Filtration Rate.
- ✚ **GIT:** Gastro-Intestinal Tract.
- ✚ **gm:** Gram.
- ✚ **HF:** Heart Failure.
- ✚ **HR:** Heart Rate.
- ✚ **hr:** Hour.
- ✚ **Htn:** Hypertension.
- ✚ **ICP:** Intra-Cranial Pressure.
- ✚ **IHD:** Ischemic Heart Disease.
- ✚ **IM:** Intra Muscular.
- ✚ **IOP:** Intra-Ocular Pressure.
- ✚ **IV:** Intra venous.
- ✚ **kg:** Kilogram.
- ✚ **LA:** Local Anesthetic.
- ✚ **LMA:** Laryngeal Mask Airway.
- ✚ **Lt:** Left.
- ✚ **MAOI:** Mono-Amino-Oxidase inhibitors.
- ✚ **MAP:** Mean Arterial Pressure.
- ✚ **mg:** Milligram.
- ✚ **μg:** Microgram.
- ✚ **MW:** Molecular Weight.
- ✚ **PR:** Peripheral Resistance.
- ✚ **Ptn:** Protein.
- ✚ **Pt:** Patient.
- ✚ **RAS:** Reticular Activating System.
- ✚ **RBF:** Renal Blood Flow.
- ✚ **RR:** Respiratory Rate.
- ✚ **Rt:** Right.
- ✚ **SBP:** Systolic Blood Pressure.
- ✚ **Sch:** Succinyl Choline.
- ✚ **SC:** Subcutaneous.
- ✚ **SVP:** Saturated Vapor Pressure.
- ✚ **ttt:** Treatment.
- ✚ **UOP: Urine Out Put.**
- ✚ **VC:** Vasoconstriction.
- ✚ **VD:** Vasodilatation.
- ✚ **VMC:** Vaso-Motor Center.
- ✚ **V_T:** Tidal Volume.
- ✚ **V_d:** Volume of Distribution.

MECHANISM OF ACTION OF GENERAL ANESTHETICS

Definition of General anesthesia: It's an altered physiological state characterized by reversible loss of consciousness, analgesia of entire body, amnesia, & some degree of muscle relaxation.

A) Lipid Solubility Theory (The Unitary Hypothesis):

Lipid solubility e.g. (Oil/gas partition coefficient) determines **Anesthetic potency** e.g. (MAC). This is called **Meyer Overton rule** as the anesthetic molecules bind at specific lipophilic sites but not all lipid-soluble molecules are anesthetics.

B) Affection of Synaptic Transmission: (RECENT)

a) Presynaptic Mechanisms: (NEUROTRANSMITTERS)

1. Chronic depolarization **i.e.** activation of presynaptic K^+ channels → **Decreased RELEASE** of neurotransmitters.
2. **Decreased** presynaptic **RELEASE** of excitatory transmitters e.g. glutamate.
3. **Increased UPTAKE** of excitatory transmitters e.g. glutamate.
4. **Decreased** Acetyl-choline **RE-SYNTHESIS** with presynaptic **DEPLETION**.

b) Postsynaptic Mechanisms: (RECEPTORS)

1. **INHIBITION** of **glutamate** receptors e.g. Ketamine & Isoflurane inhibits **N-Methyl D-aspartate (NMDA)** "subtype of glutamate receptors".
2. **INHIBITION** of nicotinic **acetyl-choline** receptors.
3. **STIMULATION** of **GABA** receptors by increasing GABA (inhibitory transmitter) which increases Cl^- influx.

INTRAVENOUS ANESTHETICS

Classification:

A) Rapidly acting:

1. Barbiturates*
 - ✓ Methyl-barbiturate
 - ✓ Thio-barbiturate (**THIOPENTONE SODIUM**)
2. Imidazole compounds e.g. Carboxylated imidazole compound (Etomidate).
3. Alkyl phenols e.g. Di-isopropyl phenol (**PROPOFOL**).

B) Slower acting:

1. Phencyclidine derivatives (**KETAMINE**).
2. Benzodiazepines e.g. **MIDAZOLAM**.
3. Large doses of opioids e.g. **FENTANYL**.
4. Neuroleptic agents (affect either dopamine receptor or dopamine itself)
 - ✓ Phenothiazines e.g. Chlorpromazine
 - ✓ Butyrophenones e.g. Droperidol, Haloperidol.
 - ✓ Thioxanthenes.
 - ✓ Reserpine.

REMARK: Neurolepto-analgesia

It's a state of analgesia with indifference to environmental stimuli without loss of consciousness which can be achieved by combining Neuroleptic (Droperidol) + Narcotic (Fentanyl) to form **Thalamonal**.

Pharmacokinetics:

A) Absorption: IV route bypasses the process of absorption.

B) Distribution:

- ▶ After IV administration the drug will be distributed to different tissues according to **Organ perfusion**, **Lipid solubility** and **Protein binding**.

- ✓ Distribution to fat is slow in spite of high lipid content due to low blood supply.
- ✓ Distribution to muscles is also slow in spite of higher blood supply due to low fat content.

- ▶ Factors regulating rate of distribution to Brain:

1. Cerebral Blood Flow (CBF): $\downarrow$ CBF $\rightarrow$ $\downarrow$ rate of delivery of the drug & subsequently its action.
2. Lipid solubility of the drug: It determines rate of BBB crossing.
3. Protein binding: (Free drug in plasma cross the BBB)
So the lower the level of binding ptns, the higher the rate of delivery as in:
 - i. Low plasma ptn level (e.g. liver & kidney diseases)
 - ii. Displacement by other drugs e.g. Salicylates
 - iii. Hyperventilation.
4. pKa* of the drug as the non-ionized fraction cross the BBB.
5. Speed of injection: rapid IV administration $\rightarrow$ $\uparrow$ speed of induction.

- ▶ Termination of drug action depends on **REDISTRIBUTION** of drug*.

C) Metabolism: Primarily in LIVER, if the drug metabolism is rapid so it shares in termination of drug action

D) Excretion: water soluble metabolites.

Pharmacodynamics: will be discussed later in table form.

REMARKS*:

- **pKa**: pH at which ionized and non ionized forms of the drug are at equilibrium.
- **REDISTRIBUTION**: After the highly perfused organs (heart, kidney, brain, and liver) are saturated during initial distribution, the low perfused organs will continue to take up the drug from the blood. As plasma concentration falls, some drug leaves the highly perfused organs to maintain equilibrium according to the concentration gradient.
- On repeated doses of drug, the low perfused organs will be saturated so, **REDISTRIBUTION** can not occur and awakening will depend upon drug elimination so rapid-acting drugs such as Thiopentone and Fentanyl will become longer acting after repeated administration or when a large single dose is given.
- **According to chemical structure Barbiturates are classified into:**

Drug	In the Barbituric ring		Characters
	Position 1	Position 2	
Oxy-barbiturate	H	O	delayed onset & prolonged action
Methyl-barbiturate	CH ₃	O	✓ Rapid onset and recovery (CH ₃) ✓ Excitatory phenomenon (CH ₃)
Thio-barbiturate	H	S	Rapid onset and recovery (S)
Methyl thio-barbiturate	CH ₃	S	✓ Very rapid onset and recovery (CH ₃ + S) ✓ Excitatory phenomenon (CH ₃)

	THIOPENTONE SODIUM	PROPOFOL	KETAMINE
Actions on CNS	It DEPRESSES THE RETICULAR FORMATION by stimulation of GABA receptors (by $\uparrow$ Cl^- influx) i.e. It potentiates GABA mediated CNS inhibition by: 1. $\uparrow$ The Duration of opening of Cl^- channel. 2. $\uparrow$ Affinity of GABA receptors to GABA. GABA receptors: it's a Pentameric structure composed of 5 subunits called (α, β, γ, δ, ρ) with the Cl^- channel in the middle: Delta & Rho (δ, ρ) are structural not functional units. - Alpha (α): it's the binding site for GABA. - Beta (β): it's the binding site for Barbiturates. - Gamma (γ): it's the binding site for Benzodiazepines and also called BZ receptors.		✓ It produces DISSOCIATIVE ANESTHESIA (rather than depression of RAS). ✓ Ketamine interacts with NMDA, opioid receptors & voltage sensitive Ca channels.
▶ Mechanism of CNS depression			
▶ CNS depression (Hypnosis)	Potent hypnotic Onset: 30 s. after IV (Depending on loss of eyelash reflex) Recovery: 5-10 min. Characterized by : - Hangover (due to cumulation). - Loss of consciousness may be delayed in cases with low COP. - Recovery may occur at high blood concentration if large dose or rapid injection due to: a. acute tolerance b. altered distribution.	Potent hypnotic Onset: 20-40 s. after IV. (Depending on loss of verbal contact, not loss of eyelash reflex as its transfer from blood to brain is slower than sodium Thiopentone). Recovery is rapid. Characterized by : - Minimal hangover. - Excitatory phenomenon may occur with induction (muscle twitching, spont. Movements, opisthotonus position, hiccup). May be due to subcortical glycine antagonism.	Potent hypnotic Onset: 30-40 s. IV 3-4 min. IM. Recovery: 10-15 min IV 15-25 min IM Characterized by : Emergence delirium with recovery (restlessness, nightmares, agitation, hallucinations) These symptoms are less common in elderly and children & can be reduced by: a. Premedication with Benzodiazepines. b. Avoidance of tactile and vocal stimulation.
▶ Analgesia	Poor analgesic With ant-analgesic effect i.e. decreases pain threshold, in sub-anesthetic dose (low dose or with recovery). This leads to postoperative restlessness.	Poor analgesic With no ant-analgesic effect.	Potent analgesic In sub-anesthetic dose with no ant-analgesic effect. The closest to be a complete anesthetic: as it produces hypnosis, analgesia, amnesia.
▶ Cerebral Metabolic Rate CPP: Cerebral Perfusing Pressure.	✓ Decreases CMR, CBF, ICP* ✓ Brain protection: provides brain protection during focal ischemia as it $\uparrow$ CPP (due to the $\downarrow$ in ICP > the $\downarrow$ in ABP).	✓ Decreases CMR, CBF, ICP* ✓ Brain protection: CPP may decrease < 50 mmHg but it provides some brain protection	✓ Increases CMR, CBF, ICP. ✓ Brain protection: NO
▶ EEG changes	Electrical Suppression.	$\downarrow$ frequency & $\uparrow$ amplitude	Loss of alpha rhythm with predominant theta activity.
▶ Other actions	- V. potent anticonvulsant. - Depression of 1. Spinal cord reflexes. 2. Sympathetic > Parasymp.	Decreases duration of seizures produced by ECT but should used with caution in epileptic pts.	Amnesia that lasts for one hour after recovery.

REMARKS*: **DISSOCIATIVE ANESTHESIA:** Functionally the thalamus (which relays sensory impulses from the RAS to the cerebral cortex) is dissociated from the limbic cortex (which is involved with the awareness of sensation).

N-Methyl-D-aspartate (NMDA): subtype of glutamate receptors.

Decreased CMR $\rightarrow$ $\downarrow$ Cerebral O_2 consumption $\downarrow$ **ICP & CBF** due to 2ry VC of cerebral vessels

Hangover effect & cumulation: Occurs if further doses are given within 24-48 hrs especially in Elderly pts.

	THIOPENTONE SODIUM	PROPOFOL	KETAMINE
Actions on CVS	Variable according to patient's volume status, baseline autonomic tone, and cardiac condition.		Is mainly due to central sympathetic stimulation & ↑ myocardial sensitivity to catecholamines
▶ ABP	Decreased* due to peripheral VD of capacitance vessels (due to -- of VMC)	Decreased up to 40% due to peripheral VD & direct myocardial dep. (-ve inotropic effect) it attenuates the Pressor response to intubation > Thiopentone.	Increased up to 25% VD in tissues with alpha R. VC in tissues with Beta R. (as sympathetic stimulation of peripheral circulation is inhibited) Hypotension may result in hypovolemic pts.
▶ HR	Bradycardia may occur (Depression of sympathetic > parasympathetic) but reflex Tachycardia occurs due to hypotension.	Changes are rare slight + + in HR but it may produce severe bradycardia up to asystole in ; - Extremes of age. - -ve chronotropic drugs. - Oculocardiac reflex. (Premedication with atropine in these patients is important)	Increased up to 20% with +ve inotropic effect . (by ↑ Ca ⁺⁺ influx by cAMP) Large doses & sympathetic blockade (βB) → direct myocardial depression due to: - Inhibition of Ca Influx. - Depletion of catecholamines.
▶ COP	Maintained by* : - Reflex tachycardia. - ↑ Myocardial contractility. - Slight increase in the PR due to peripheral VC of resistance vessels.	Maintained as Thiopentone	Increased with ↑ cardiac work so it's better avoided in - IHD. - Uncontrolled Htn. - Congestive HF.
Actions on Respiration			
▶ Resp. center(RC)	✓ Depression with decreased sensitivity to hypercapnia & hypoxia. ✓ Apnea for short periods.	✓ Depression is more. ✓ Apnea for longer periods.	✓ Maintained . ✓ Apnea rarely occurs in large IV doses.
▶ Upper airway reflexes.	✓ Slight depression . ✓ Laryngeal spasm is precipitated by surgical stimulation, FB & secretions in upper airways due to slight depression of reflexes	✓ Potent depression . ✓ Laryngeal spasm is uncommon due to potent dep. of reflexes (it's the most suitable drug with LMA).	Maintained but there presence can't be guaranteed.
▶ Bronchial muscle tone	Increased (due to histamine release or direct action on bronch. mus.) May → bronchospasm in asthmatic pts.	NO effect	Potent bronchodilatation .
Actions on GIT		Antiemetic effect	✓ Postoperative nausea & vomiting. ✓ ↑ salivation. (premedication with atropine is important)
Actions on Skeletal muscles	✓ Decreased tone due to inhibition of spinal cord Reflexes. ✓ Movement in response to surgical stimulation is common.		✓ Increased tone . ✓ Spont. Movements are common (but not due to surgical stimulation).

REMARKS*: Wide BP swings occurs in patients with poorly controlled hypertension **this can be reduced by** slow injection of Intraval, preoperative hydration.

Baroreceptors are responsible for maintaining COP by releasing the medullary pressor area from inhibition → ↑HR, +ve inotropism, ↑PR. Inadequate baroreceptor response (as in hypovolemia, βB, congestive HF) → ↓COP, ↓ABP, unmask the direct myocardial inhibition.

	THIOPENTONE SODIUM	PROPOFOL	KETAMINE
Actions on Eye	✓ IOP : ↓ by 40% ✓ Pupil: dilate then constricts. ✓ Reflexes: are lost (corneal, conjunctival, eyelash & eyelid).	Disappearance of eyelash reflex is delayed so if it's used as a clinical sign for loss of consciousness → Overdose.	✓ IOP: transient increase. ✓ Eye movements are persistent.
Actions on Uterus	✓ Ordinary doses have little effect on tone while large doses → ↓ uterine cont. ✓ Crosses placental barrier		Crosses placental barrier → Fetal conc. = Maternal conc.
Actions on Hepato-renal functions	✓ Transient impairment of functions as it ↓ their blood flow ✓ It's enzyme (cp 450) inducer (it increases metabolism & elimination of other dugs).	✓ Transient impairment of RBF. (Less than Thiopentone). ✓ ↓ Hepatic blood flow but no change in liver function tests after 24 hrs. infusion.	
Other actions	Induces histamine release (as it contains sulfur group)	✓ Antipruritic action. ✓ Lowers plasma cortisol level.	Skin rashes have been reported.
Dosage & Routes of administration	✓ IV: 2.5% sol. is recommended <u>Dose for induction:</u> - For children 6 mg/kg. - For adult 4 mg/kg. - For elderly 2.5-3 mg/kg. <u>Sedative dose:</u> 0.5-1.5 mg/kg <u>Precautions with injection:</u> - Small vol. (2 ml of 2.5% sol) is given slowly & the pt. is asked if he felt pain to avoid intra-arterial inj. - Induction should be slow especially cardiac pts. ✓ RECTAL: 5-10% sol. <u>Dose:</u> 25-44 mg/kg. <u>To induce Basal narcosis (sleep) in children within 10-15min.</u>	✓ IV: <u>Dose for induction:</u> - For children 3-3.5 mg/kg. - For adult 1.5-2.5 mg/kg. - For elderly 1.25 mg/kg. + shot of 10 mg till loss of consciousness. <u>Precautions with injec.:</u> - Not recommended < 3 yrs - The dose is lowered in premedicated pts. - Slow Induction ↓ CVS side effects. ✓ IV infusion: <u>For maintenance:</u> Multi-step infusion regimen 10 mg/kg for the 1 st 10 min. 8 mg/kg for the 2 nd 10 min. 6 mg/kg till the end. <u>For sedation:</u> 2-4 mg/kg/hr during regional anesthesia, endoscopy & in ICU.	✓ IV: <u>Dose for induction:</u> 2 mg/kg <u>Analgesic dose:</u> without loss of consciousness. 0.25-0.5 mg/kg Or 50 µg/kg/min . <u>Precautions with injec.:</u> - Additional doses are needed 1-1.5 mg/kg every 5-10 min. - The dose is lowered in elderly & shocked pts. - Induction should be slow. ✓ IM: 5-10 mg/kg ✓ Oral: 5-10 mg/kg
Uses	1. Induction of anesthesia. 2. Maintenance of anesthesia. 3. Basal narcosis. 4. ttt of status epilepticus. 5. Decreases ICP.	1. Induction of anesthesia esp. in outpatient cases & when rapid recovery is needed. 2. Maintenance of anesthesia. 3. Sedation during regional anesthesia & endoscopy & in ICU.	1. Induction of anesthesia in - High risk pts (shocked pts). - Asthmatic pts. - Pediatrics (minor surgery, ophthalmic examination). - Difficult locations (wars, accidents). - Developing countries. 2. Analgesia in Painful dressing, positioning of pt with pain before regional anesthesia. 3. Sedate asthmatic pt in ICU.

	THIOPENTONE SODIUM	PROPOFOL	KETAMINE
Side effects			
▶ CNS	1. Drowsiness that persists for 24-36 hrs. 2. No emergence or excitatory phenomena.	1. Excitatory phenomena. 2. No emergence phenomena. 3. Convulsions may occur in epileptic pts.	1. Emergence & excitatory phenomena. 2. Increases ICP. 3. Prolonged recovery.
▶ CVS	<u>Hypotension</u> due to VD - Especially in (Hypovolemia, Hypertension, Cardiac diseases). - Precautions: a) Preoperative Hydration. b) Slow injection c) Never in sitting position.	<u>CVS depression</u> due to VD & -ve inotropic effect - Especially in (Hypovolemia, Hypertension, Cardiac diseases). - Precautions: a) Preoperative Hydration. b) Slow injection c) Never in sitting pos. Produces CVS depression > any other barbiturates.	1. Hypertension. 2. Tachycardia.
▶ Respiration	1. Respiratory depression due to ↓ RC - Especially in (Myasthenia, Myotonia dystrophica, excessive doses, receiving opioids). - Precautions: a) Slow injection. b) Artificial airway facilities. 2. Laryngeal spasm. 3. Bronchospasm in asthmatic pts may occur.	<u>Respiratory depression</u> Produces respiratory depression > barbiturates.	
▶ Allergy	P R E S E N T		
▶ During injection	A) Intra-venous: Pain & Thrombophlebitis esp. in small veins. B) Peri-vascular: extravasation - Tissue necrosis occurs (SC tissues) - Median N. damage may occur in antecubital fossa. - Management: 1. Leave the cannula in place. 2. Hyaluronidase injection. C) Intra-arterial: - Picture: 3b ▪ Severe BURNING PAIN. ▪ Forearm & hand may BLANCH & show BLISTERS distally. - Mechanism: ▪ VC. ▪ Local release of noradrenalin. ▪ Formation of emboli*. - Treatment: ▪ Stop inj. if there is any pain. ▪ Leave the cannula in place & inject Papaverine 20mg ▪ Stellate gang. or brachial plexus block. ▪ IV heparin & oral anticoagulant.	A) Intra-venous: - More Pain esp. in small veins. - Avoided by injection of 10 mg Lignocaine just before it OR mixing 10 mg Lignocaine with it before injection. - No thrombophlebitis. B) Peri-vascular: NO C) Intra-arterial: NO	NO
▶ Others		Long-term sedation of children in ICU → Lipemia, Metabolic acidosis, Death.	1. Salivation. 2. Postoperative nausea & vomiting.

REMARK*: Formation of emboli: Due to formation of thiopental crystals, endarteritis & ATP released from damaged cells → platelet aggregation.

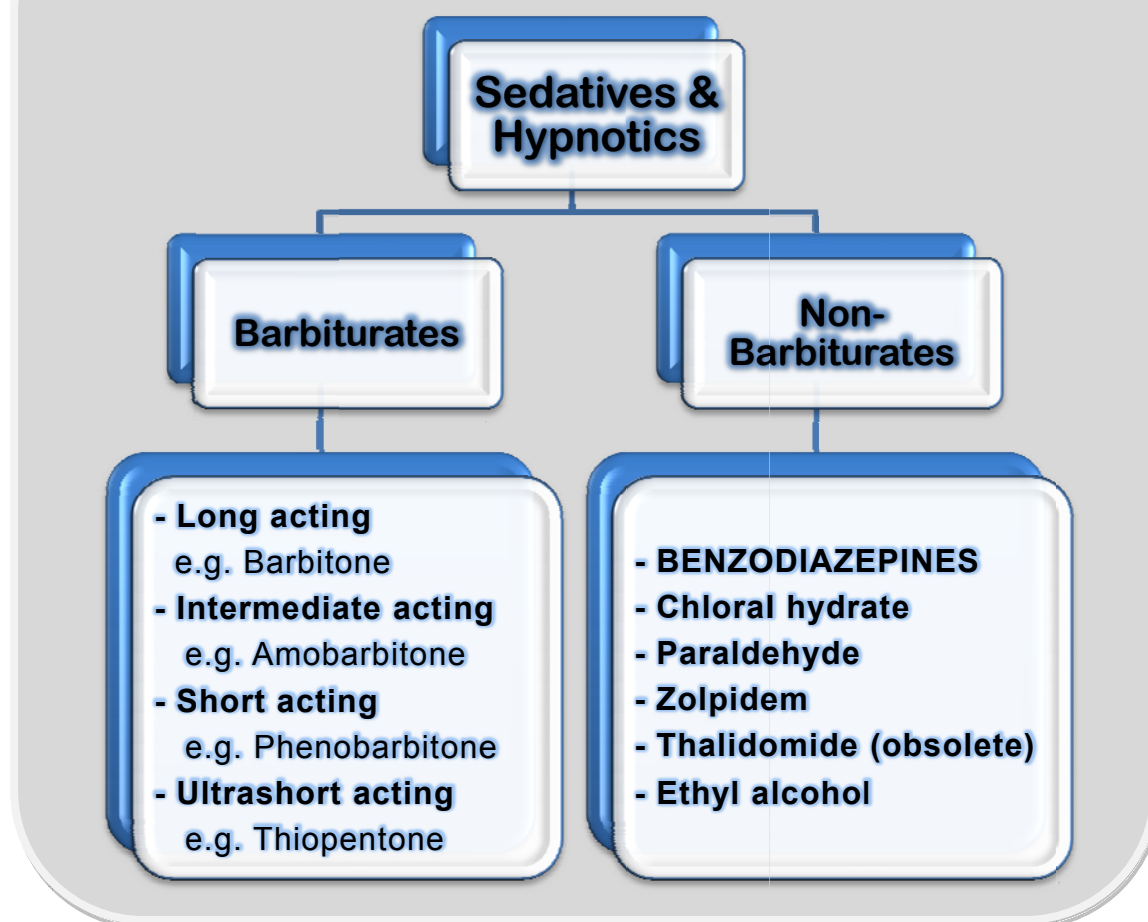
	THIOPENTONE SODIUM	PROPOFOL	KETAMINE
Contraindications ► Absolute ► Relative (can be used but with special care)	Airway obstruction. Hypersensitivity. Porphyria: It ↑ production of porphyrins → LMNL &/or CVS collapse. A. CNS: Outpatient anesthesia NOT suitable Due to slow recovery & drowsiness. B. CVS: (see CVS side effects) C. Respiratory diseases: - Bronchial asthma. - Muscle diseases → more respiratory depression. D. Renal diseases: (CRF) ↓ Ptn binding (excretion isn't affected). Normal dose is given but V. slowly. E. Hepatic diseases: ↓ Ptn binding & impaired metabolism (has little effect on recovery). Normal dose is given but V. slowly. F. Metabolic status: Pts with low metabolic rate (Myxedema, Adrenocortical insufficiency, extremes of age). G. Pregnancy: Give Adequate dose to the mother however, excessive dose → Fetal resp. & CVS depression esp. if Induction-Delivery duration was short.	Airway obstruction. Hypersensitivity. Children < 1 month. Long-term sedation of children in ICU. (Safe in Porphyria). A. CNS: Outpatient anesthesia More suitable than barbiturates. B. CVS: Less suitable than barbiturates	Airway obstruction. ↑ ICP. A. CNS: Outpatient anesthesia NOT suitable Due to Prolonged recovery & Emergence phenomena B. CVS: NOT suitable for - IHD. - Uncontrolled Htn. - Congestive HF. C. Poorly suppress response to Visceral Stimulation so add opioids if visceral stimulation is anticipated. D. Not suitable for frequent procedure: due to prolonged recovery & it disturbs sleep & eating on repeated administration.
Drug interaction	- It is enzyme inducer (cytochrome P 450) i.e. it increases metabolism & elimination of other dugs. β blockers Potentiate CVS depression. Other CNS depressants potentiate its sedative effect e.g. Narcotics. - Drugs that displace Thiopentone from ptn binding sites → ↑ its free form → ↑ systemic side effects e.g. sulfonamides.	- Fentanyl & Alfentanil concentrations may ↑ by concomitant administration of Propofol. - Previous formulation containing Cremophor E1 (not in new formulation) → ↑ non-depolarizing muscle relaxants.	Non depolarizing muscle relaxant → potentiation. Theophylline may → seizures Diazepam → attenuates Ketamine cardio-stimulatory effect & its elimination $t_{1/2}$ Sympathetic antagonists as α & β blockers will unmask the direct myocardial depressant effect of Ketamine. Lithium: prolongs duration of Ketamine. Halothane, benzodiazepines or barbiturates → ↓ distribution & clearance → prolonged action. Halothane and other volatile agents → potentiate myocardial depression.

E X T R A S

	THIOPENTONE SODIUM	PROPOFOL	KETAMINE
Physical properties	▪ pKa. 7.6 ▪ pH 10.8 ▪ Solubility: - Lipid soluble (so, it crosses BBB). - Mixed with 6% anhydrous Na carbonate (to ↑ its water solubility). ▪ Storage: - Stored in nitrogen (to prevent chemical reaction with atmospheric CO₂). - Short shelf life. - freshly prepared solution is stable for 2 weeks, but manufacturers recommend storing for 24 hrs only as it contains no antibacterial preservatives ▪ Shape: Yellowish powder in Vials (500 or 1000 mg) with a bitter taste and faint smell of garlic.	▪ Solubility: Highly lipid soluble (not water soluble). ▪ Storage: - Long shelf life. - It should be used completely within 6 hrs of opening the ampoule with good sterile techniques because it contains no antibacterial preservatives. ▪ Shape: white aqueous oil in Ampoules 20mL (10 mg/ml) (1%). ▪ Previously, it was formulated in Cremophor EI which → histamine release & anaphylactic reaction and potentiates muscle relaxant. Now, It is white aqueous oil in water emulsion containing soya bean oil & purified egg phosphatide (egg lecithin).	▪ pKa. 7.5 ▪ pH 3.5 - 5.5. ▪ Solubility: Extremely lipid soluble (also water soluble). ▪ Storage: - Long shelf life. - Contains NaCl to be isotonic. - Contains benzethonium chloride 0.1mg/ml as a preservative. ▪ Shape: Clear solution in Multi-dose vials: 10 ml (50-100 mg/ ml).

METHOHEXITONE SODIUM	ETOMIDATE
▶ CNS actions: As Thiopentone+ EEG may show in epileptic pts. Epileptic form activity. ▶ CVS actions: As Thiopentone ▶ Respiratory actions: As Thiopentone+ no bronchial muscle effect. ▶ Neuromuscular actions: As Thiopentone. ▶ Hepatorenal & Ocular action: As Thiopentone. ▶ SIDE EFFECTS: As Thiopentone + ▪ Excitatory phenomenon ▪ EEG may show in epileptic pts. Epileptic form activity. ▪ During injection: complications are more sever. ▶ CONTRAINDICATIONS: As Thiopentone	▶ CNS actions: As Thiopentone + ▪ Excitatory phenomenon due to the disinhibitory effect on areas controlling the extra Δ system. ▪ Not used in brain protection due to the neurotoxic effect of propylene glycol (additive to make preparations water soluble). ▶ CVS actions: Least agent with CVS effect (slight hypotension). ▶ Respiratory actions: Least depression + no bronchial muscle effect. ▶ Neuromuscular actions: As Thiopentone. ▶ Endocrinal action: ▪ After single induction dose → inhibition of enzymes in adrenal gland → ↓cortisol & aldosterone synthesis. ▪ After long term infusion → impairment of response to adreno-cortico-trophic hormones → ADRENOCORTICAL SUPPRESSION. ▶ SIDE EFFECTS: As Thiopentone + ▪ Excitatory phenomenon. ▪ ADRENOCORTICAL SUPPRESSION. ▪ During injection pain is more sever but there is NO effect if injected Intra arterial or perivascular. ▶ CONTRAINDICATIONS: As Thiopentone

CLASSIFICATION OF SEDATIVE & HYPNOTICS



BENZODIAZEPINES

Used as **sedative hypnotic**, although it can produce anesthesia in large doses

Classification:

- **Long acting:** DIAZEPAM (Valium, Neuril), Clorazepate. ($t_{1/2} > 24$ hrs).
- **Intermediate acting :** Lorazepam (Ativan), Alprazolam (Xanax) ($t_{1/2}$ 6-24 hrs)
- **Shot acting:** MIDAZOLAM (Dormicum). ($t_{1/2} < 6$ hrs).

Pharmacodynamics:

► Mechanism of action:

- a. Site of action: Polysynaptic pathways in the spinal cord & Brain especially in
 1. **Midbrain Reticular formation.** (responsible for wakefulness)
 2. **Amygdala Area of limbic system.** (responsible for expression of emotions including anxiety)
- b. Mode of action: By interaction with benzodiazepine receptors in the CNS facilitating inhibitory neurotransmitters as GABA to bind to its receptor which ↑ **Frequency** of Cl^- passage through channels.
- c. Types benzodiazepine receptors: (this is γ subunit of GABA receptors which has 2 subtypes A & B) BZ_1 & BZ_2
 - BZ_1 responsible for anxiolytic, sedative & hypnotic effects.
 - BZ_2 responsible for muscle relaxant & anticonvulsant effects.

REMARK: FLUMAZENIL: Is benzodiazepine-receptor antagonist, can be given orally or IV to reverse most CNS actions of BENZ. , **DOSE:** 0.3-1mg which can be repeated after 1-2 hrs due to rapid hepatic clearance OR 0.5 mg/hr for IV infusion (which is useful in overdose by long acting BENZ.)

► Actions:

A) Actions on CNS:

1. **SEDATION** (which is progressive & dose dependent i.e. progress to stupor & loss of consciousness at induction doses), **AMNESIA** (which is anterograde), **ANXIOLYSIS** (useful as premedication).
2. **NO** analgesic effect.
3. **Cerebral Metabolic Rate (CMR): decrease** CBF, Cerebral O₂ Consumption & ICP (Not to the extent as barbiturates).
4. **Anti convulsant effect:** Benz. Doesn't affect the seizure focus but prevent subcortical spread of seizure activity.
5. **Dependence** after chronic administration.

B) Actions on CVS: (large doses)

- Decreased **ABP & PR**.
- Decreased **COP**.
- Increased **HR** reflexly.

C) Actions on Respiration:

1. **Depression of ventilatory response** to CO₂ which is usually insignificant unless:
 - Given intravenously.
 - Large doses.
 - Given with other resp. depressants.
 - In Elderly & debilitated pts.
2. **Apnea** may occur but it's less common than barbiturates.
3. **Upper airway obstruction** may occur as a result of loss of consciousness.

D) Actions on Skeletal Muscles: mild muscle relaxation which mediated at the spinal cord not at the neuromuscular junction (not sufficient for surgery).

E) Actions on Uterus: crosses the placental barrier rapidly → neonatal depression.

► Uses:

1. Anesthetic supplementation.
2. Premedication of anesthesia.
3. Cardio-version.
4. Dentistry.
5. Endoscopy
6. Sedation in ICU.

► Side effect:

1. Residual drowsiness.
2. Impairment of mental function.
3. Ventilatory depression.
4. Nausea, Vomiting & Vertigo.
5. Ataxia, Dysarthria.
6. Addiction (on chronic use)
7. Allergy.

► Advantages over Barbiturates:

1. More selective on CNS.
2. More safety margin.
3. Less CVS & Resp. side effects.
4. Less Addiction.
5. Less Tolerance.
6. Fewer drug interaction.
7. No Hangover.
8. No enzyme induction.

REMARKS:

Drug interactions:

1. Cimetidine reduces Diazepam metabolism.
2. Erythromycin inhibits metabolism of Midazolam and increases the duration & intensity by 2-3 folds.
3. Heparin displaces Diazepam from ptn binding sites → ↑ its free form.

	DIAZEPAM	MIDAZOLAM
► Physical properties	- Relatively lipid soluble & water insoluble. - Propylene glycol is added to make it water soluble which → thrombophlebitis	Water soluble (due to its imidazole ring)
► Kinetics	Absorption (if given orally): rapid Distribution: To highly perfused organs esp. Brain than less perfused organs. Metabolism: by liver microsomal enzymes → <u>active metabolites</u>. Excretion: excreted conjugated with glucuronic acid.	Absorption bypassed by the parenteral route. Distribution: To highly perfused organs esp. Brain than less perfused organs. Metabolism: by liver microsomal enzymes → <u>inactive metabolites</u>. Excretion: excreted conjugated with glucuronic acid.
► Dosage & Routes of administration	- Given orally and IV (its oral bioavailability is 100%) - Can be given rectally. - IM route: slow, erratic & incomplete absorption. DOSAGE: - Premedication (oral): 0.2-0.5 mg/kg (maximum dose 15 mg) 1-5 mg in children - Sedation (IV): 0.04-0.2 mg/kg slowly. - Induction (IV): 0.3-0.6 mg/kg. - ICU (IV): Bolus 5-15 mg (no infusion). - Status epilepticus: 10-20 mg IV / 5min. repeated after 30 min. if necessary.	- Given IM and IV. DOSAGE: - Premedication (IM): 0.07-0.15 mg/kg (2.5 mg in elderly) - Sedation (IV): 0.01 - 0.1 mg/kg. - Induction (IV): 0.1 - 0.4 mg/kg. - ICU (IV): Bolus of 5-10 mg followed by infusion of 1-20 mg/hr
► Actions	- Onset: after IV bolus → sedation within 1-2 min., after oral route → effective within 30-45 min. ACTIONS: the same + transient analgesia after IV route.	- Onset is more rapid & duration is shorter than Diazepam. - Midazolam / Diazepam potency is 1.5 - 2 / 1 ACTIONS: the same but NOT recommended as anti-convulsant. Advantages: - Shorter duration so there is less residual mental impairment. - Low incidence of thrombophlebitis. Disadvantages: - Ventilatory depression in elderly. - CVS depression in hypovolemic pts.

REMARK:**Chloral hydrate (Chloral):**

- Duration of action:** 6-8 hours.
- Advantages:** minimal hangover & respiratory depression.
- Side effects:** Gastric mucosal irritation, confusion, nightmares.
- Contraindications:** Peptic ulcer and Liver & Kidney diseases.
- Toxicity:** Acute: vomiting, Pin point pupil, Resp. Dep. Chronic: Tolerance & Addiction.
- Dose:** Hypnotic dose: 0.5 – 2 gram Sedative dose: 250mg
In children: 50 mg/kg (Maximum daily dose 1gm)
It's given by a teaspoon = 5 cc = 500 mg.

INHALATIONAL ANESTHETICS

Classification:

- ✓ Halothane.
- ✓ Isoflurane.
- ✓ Sevoflurane.
- ✓ Enflurane
- ✓ Desflurane
- ✓ Ether
- ✓ Methoxyflurane.
- ✓ Nitrous Oxide.

Pharmacokinetics:

A) Factors Affecting Inspiratory Concentration (Fi):

- ✓ **Increasing** fresh gas flow rate.
 - ✓ **Decreasing** the volume of the breathing system.
 - ✓ **Decreasing** the absorption by anesthetic machine of the breathing system.
- These results in the inspired gas conc. will be closer to Fresh gas conc.**

B) Factors Affecting Alveolar Concentration (FA):

Alveolar conc. is the principal factor in determining Onset of action.

1. **UPTAKE:**

- ▶ Uptake of the anesthetic gas by the body → ↓ in the Alveolar gas concentration which in turn become less than the Inspiratory gas conc. so the greater the uptake of the anesthetic gas:
 - The greater the difference between inspired & alveolar concentrations.
 - The lower the rate of rise of the alveolar concentration & partial pressure.
 - The slower the rate of induction & also recovery.

▶ Factors affecting **UPTAKE:**

a) Solubility in Blood:

Anesthetic agents with low solubility coefficient e.g. N₂O will be **less TAKEN UP** by the body → ↑Alveolar gas conc. → higher rate of induction.

REMARK: The relative solubilities of an anesthetic in air, blood & tissues are expressed as partition coefficient, each coefficient is the ratio the concentrations of the anesthetic gas in each of 2 phases (e.g. blood & alveoli) at the same Temp., volume & equal partial pressures in the 2 phases.

b) Alveolar blood flow :

It's equal to COP (In absence of pulmonary shunting) so, if COP is ↑ → ↑alveolar blood flow → ↑**UPTAKE**.

REMARK: Low COP states → over dosage as the alveolar conc. is markedly increased.

c) The difference between ALVEOLAR GAS PARTIAL PRESSURE & VENOUS BLOOD PARTIAL PRESSURE:

The difference between partial pressures creates a Gradient upon which the pulmonary uptake depend, however this gradient depends on SYSTEMIC (tissue) uptake which is affected by

- Tissue Solubility of Gas.
- Tissue blood flow.
- The difference between tissue partial pressure & arterial blood partial pressure.

This gradient will be absent if there was no systemic (tissue) uptake which will lead to no pulmonary uptake.

- #### 2. **VENTILATION:** Increasing the ventilation causes increased delivered concentrations of anesthetics to the alveoli maintaining alveolar concentration causing more rapid onset of induction.

3. **CONCENTRATION:** Increasing the conc. of inspired anesthetic (by the conc. dial of the Vaporizer) increases the rate of induction. This occurs through 2 effects:

- **The CONCENTRATING effect:** Increasing the conc. of inspired anesthetic increases the alveolar conc. of anesthetic gas and subsequently the rate of induction. (the concentration effect of one gas on another is called **2nd GAS EFFECT**)
- **The AUGMENTED INFLOW effect:** After the pulmonary uptake, anesthetic mixture is added to the remaining alveolar conc. → ↑ the alveolar conc.

4. **Breathing system dead space:** its decrease → ↑ the rate of rise of alveolar conc.

C) Factors affecting arterial concentration (Fa):

Ventilation/Perfusion (V/Q) Mismatch

Normally it's assumed that Arterial & Alveolar anesthetic partial pressures are equal but in fact arterial partial p. is at lower level due to

- Venous admixture.
- Alveolar dead space.
- Non-uniform alveolar gas distribution.

Presence of Ventilation/Perfusion Mismatch → ↑ Alveolar-Arterial difference i.e.

Increase in Alveolar partial pressure (esp. for highly soluble agents) &

Decrease in Arterial partial pressure (esp. for poorly soluble agents).

D) Factors affecting Elimination:

► Means of elimination of volatile anesthetics are:

1. Biotransformation (Metabolism): by Cytochrome P 450 (CYP 450) group of enzymes (especially CYP 2E1) in the liver.
2. Transcutaneous loss (insignificant).
3. Exhalation (the most important factor).

► Factors that speed up elimination and recovery (also rate of induction):

1. **Increasing** Fresh gas flow.
2. **Increasing** Cerebral blood flow.
3. **Increasing** Ventilation.
4. **Decreasing** vol. of breathing system.
5. **Decreasing** anesthetics absorbed by the machine.
6. **Decreased** solubility.
7. Elimination of rebreathing.

Pharmacodynamics

► **Mechanism of action** (See mechanism of action of General Anesthetics).

► **MAC (MINIMUM ALVEOLAR CONCENTRATION):**

▪ **Definition:** It's the alveolar concentration that prevents movement of 50% of pts. in response to a standard stimulus e.g. surgical incision.

▪ **Significance:**

1. It represents the brain partial pressure of volatile anesthetic.
2. It allows comparison between potencies of volatile anesthetic.
3. It represents a point on the dose response curve "it is equivalent to the Median effective dose (ED₅₀)".
4. Roughly the MAC values of volatile anesthetics for the CNS depressive effect are additive e.g. A mixture of ½MAC of N₂O & ½MAC of Halothane produce CNS depression which is nearly Equal to 1 MAC of Isoflurane (but this is not applicable to the Myocardial depressive effect).

▪ **Other definitions:**

1. **1.3 MAC:** It's the alveolar concentration that prevents movement of 95% of pts. in response to a standard stimulus e.g. surgical incision. (An approximation of ED₉₅) e.g. 1.3 MAC for Halothane = 1.3 x 0.74% = 0.96%.
2. **MAC-BAR (1.7-2 MAC):** It's the alveolar concentration that prevents Autonomic reflexes to painful stimuli.
3. **MAC-awake (0.2-0.5 MAC):** It's the alveolar concentration which is associated with awakening of anesthesia.

- MAC values of some volatile anesthetic:

Volatile anesthetic	Halothane	Isoflurane	Sevoflurane	Nitrous oxide
MAC (%)	0.74	1.15	1.7	104

- Factors affecting MAC:

1. Age:

- Young: Increase (Highest MAC is found in Infants 6-12 months).
- Elderly: Decrease (MAC decreases by 6% per decade).

2. Alcohol:

- Chronic abuse: Increase.
- Acute intoxication: Decrease.

3. Anemia: Decreases if the Hematocrit is < 10%.

4. Body temperature:

- Hypothermia: Decrease (MAC decreases by 2-5% per 1°C).
- Hyperthermia: Decrease (Increases if > 42°C).

5. Blood pressure: Decreases if MAP is < 40 mmHg.

6. PaO₂: Decreases if it was below 40 mmHg.

7. PaCO₂: Decreases if it was above 95 mmHg.

8. Conception (Pregnancy): Decrease (it becomes normal by 72 hr post partum).

9. Drugs:

- Decreasing MAC: Local Anesthetics except cocaine, Barbiturates, Ketamine, Benzodiazepines, Opioids, Sympatholytics and chronic Amphetamine abuse.
- Increasing MAC: Cocaine, Sympathomimetics except chronic Amphetamine abuse, Acute Amphetamine Intoxication.

10. Endocrine: THYROID hormonal disturbance (Hypo or Hyper) has no effect.

11. Electrolytes:

- Hypercalcemia: Decrease.
- Hyponatremia: Increase.
- Hyponatremia: Decrease.

- ▶ The rest of the will be discussed in table form.

REMARK:

	HALOTHANE	ISOFLURANE	SEVOFLURANE
Physical properties			
▶ MW	197.4	114.3	200.1
▶ SVP	32 (Halothane and Isoflurane can be used in the same vaporizer due to the same Saturated Vapor Pressure).		21
▶ Boiling p.	50	49	58.9
▶ Blood/Gas Coef.	2.3	1.4	0.59
▶ Oil/gas Coefficient	220	97	55
▶ Color	Colorless	Colorless	Colorless
▶ Smell	Pleasant	Pungent	Pleasant
▶ Flammable	Flammable	Non	Non
▶ Stability	Decomposed by light (stored in opaque container) Decomposed by soda lime (stored in 0.01% thymol → acute lung injury so vaporizer should be evacuated every 2-3 weeks) Corrodes metal in breathing systems in presence of moisture (corrodes AL, Lead)	Stable : so it doesn't require preservatives	In presence of water & soda lime → hydrolysis, so it is arguable in closed circuits Stored in opaque container With no preservatives.

	HALOTHANE	ISOFLURANE	SEVOFLURANE
Onset	Relatively rapid induction (less than Isoflurane).	Rapid induction (limited use due to its odor) & recovery	Rapid induction & rapid recovery but slower than Desflurane
Actions on CNS			
▶ Cerebral blood flow CBF	Increased due to ↓cerebral vascular resistance <i>Cerebral Auto-regulation, which within limits maintains CBF during BP swings, is suppressed.</i>	Increased but less than halothane. <i>Cerebral O₂ requirements are decreased.</i>	Similar to halothane
▶ ICP	Increased , however this can be prevented by hyperventilation.	Increased but less than halothane (however hyperventilation isn't necessary).	
▶ EEG	Silent	Silent	
Actions on CVS			Similar to Isoflurane
A) Heart:			
▶ Contractility	Depressed (due to interference with Na ⁺ - Ca ⁺⁺ exchange & intracellular Ca ⁺⁺ utilization)	Minimal change	Minimal change
▶ Rt. Atrial pressure	Increased (due to depression of myocardial contractility)	Minimal change	Minimal change
▶ Heart rate	Decreased (due to suppression of reflex tachycardia caused by hypotension this is due to interference with baroreceptors)	Increased (reflex tachycardia due to hypotension)	Less tachycardia
▶ COP	Decreased (due to depression of myocardial contractility)	Minimal change	Minimal change
▶ Rhythm	▪ Arrhythmogenic as it increases myocardial excitability (which is augmented by Hypoxia, Hypercarbia, ↑circulating catecholamines) ▪ Bradycardia (due to the mentioned reason above + slowing of SA node conduction)	Less arrhythmia.	
B) Blood vessels:			
▶ ABP	Decreased (due to myocardial depression and ↓ COP)	Decreased (due to stimulation of β receptors → peripheral VD)	Mild decrease
▶ vascular resistance	Minimal change	Decreased (due to peripheral VD)	Mild decrease
▶ Coronary circulation.	▪ Coronary vasodilator. ▪ Decreases coronary BF. ▪ Decreases myocardial O₂ demand.	▪ Coronary vasodilator. ▪ Coronary steal phenomenon: Dilatation of normal coronaries may divert the blood from stenotic lesion which will aggravate myocardial ischemia during Tachycardia or Hypotension.	Less Coronary vasodilator.

REMARK*: Halothane effect on COP: A) During Mechanical ventilation: Decreased due to depression of myocardial contractility which → ↓BP & ↑CVP (Rt. atrial p.). B) During Spontaneous breathing: small increase in PaCO₂ → decreased peripheral vascular resistance → Sympatho-adrenal stimulation → shift of COP to baseline.

	HALOTHANE	ISOFLURANE	SEVOFLURANE
Actions on Respiration ▶ Resp. depression ▶ Upper airway reflexes. ▶ Bronchial muscle tone. ▶ Mucociliary function	▪ Mechanism: - Central: Medullary depression. - Peripheral: Intercostal muscle dysfunction. ▪ Factors affecting it: - Augmented by: Preexisting pulmonary disease. - Attenuated by: Surgical stimulation. ▪ Results: - Rapid shallow breathing (Decreased tidal volume & Increased respiratory rate), however the increased rate is not sufficient to meet the decrease in tidal volume. - Apneic threshold, which is the highest PaCO₂ at which the pt. remains apneic, is increased. - Hypoxic drive is severely depressed. Isoflurane: there is less tachypnea → more respiratory depression & its Pungent odor → coughing & breath holding so it's avoided during induction in children. Upper airway reflexes are attenuated. Relaxation of bronchial smooth muscles (due to interference with intracellular Ca⁺⁺ utilization) → Bronchodilatation (which is more with Halothane) that can't be blocked by β-blockers. Depression of clearance of mucus from the respiratory tract → postoperative atelectasis and hypoxia.		
Actions on Skeletal muscles	▪ Relaxation of skeletal muscles. (dose dependent) ▪ Potentiation of NMB. ▪ Triggers malignant hyperthermia. ▪ Post operative shivering → ↑O₂ consumption → hypoxia unless O₂ is given.	The same but produces more potent relaxation.	The same but produces more potent relaxation esp. in children during inhalational induction of anesthesia.
Actions on GIT	↓ GIT Motility		
Actions on Uterus	Dose dependent uterine relaxation (↑blood loss & postpartum hemorrhage).		
Actions on Liver	DECREASE Hepatic blood flow (HBF).		HBF is maintained by: the portal vein blood flow is decreased but the hepatic artery blood flow is increased.
Actions on Kidney	DECREASE: RBF , GFR , UOP		
Side effects	1. Hepatotoxicity (discuss) 2. Arrhythmia. 3. Malignant hyperthermia. 4. ↑ ICP 5. Post operative shivering 6. Poor Analgesia	1. Pungent odor so it's unsuitable for inhalational induction of anesthesia. 2. Coronary steal phenomenon (discuss).	1. ↑ ICP. 2. Malignant hyperthermia. 3. Halo-alkene nephrotoxicity.
Contraindications	1. Hepatic patients 2. Arrhythmia 3. Used with caution in : i. Intracranial mass. ii. Hypovolemic patients. iii. Pheochromocytoma. iv. Cardiac patients as aortic stenosis may not tolerate the -ve inotropic effect.	1. There is no unique contraindication except the controversy about Coronary steal phenomenon. 2. Hypovolemic pts may not tolerate its vasodilating effect.	1. Intracranial mass. 2. Hypovolemic patients. 3. Malignant hyperthermia.

	HALOTHANE	ISOFLURANE	SEVOFLURANE
Advantages	1. Rapid smooth induction. 2. Minimal stimulation of salivary & bronchial secretions. 3. Bronchodilatation. 4. Skeletal muscle relaxation.	1. Rapid recovery. 2. Less hepatotoxicity. 3. Less arrhythmia. 4. Less $\uparrow$ in ICP. 5. Skeletal muscle relaxation.	1. Rapid recovery. 2. Less hepatotoxicity. 3. Less arrhythmia. 4. Skeletal muscle relaxation.
Drug interactions	1. Potentiates effect of muscle relaxants . 2. Sensitizes the heart to the arrhythmogenic effect of: Aminophylline & Adrenaline (esp. doses above 1.5 $\mu\text{g/kg}$). 3. Tricyclic antidepressant & MAO inhibitors $\rightarrow$ fluctuations in BP and arrhythmia. 4. Increases the myocardial depressive effect of βB & Ca^{++} channel blockers .	1. Potentiates effect of muscle relaxants . 2. Adrenaline can be given safely in doses up to 4.5 $\mu\text{g/kg}$.	Potentiates effect of muscle relaxants .

REMARK: Tricyclic antidepressants inhibit the uptake of catecholamines while MAO inhibitors inhibit their destruction.

TOXICITY

A) Hepatotoxicity:

- ▶ It occurs especially with Halothane and to lesser extent Methoxyflurane, Enflurane & Isoflurane.
- ▶ **Incidence:**
 - Rare in pediatrics.
 - More common in: Females, Middle age, obese pts & pts with history of exposure 28 days ago.
- ▶ **Two types of hepatic dysfunction may occur:**
 1. **Type 1, Subclinical type (Mild type):**
 - **Incidence:** More common than type 2
 - **Features:** Derangement in Liver function tests which is transient & resolve within few days.
 - **Mechanism:** Glutathione transferase increases due to reductive metabolism of Halothane in liver which react with Hepatic macromolecules $\rightarrow$ centri-lobular necrosis which is worsened by hypoxia.
 - There are reported cases after exposure to Enflurane & Isoflurane.
 2. **Type 2, Clinical type (Severe type):**
 - **Incidence:** Extremely rare.
 - **Features:** Severe jaundice that progress to severe fulminant hepatic necrosis (mortality rate 30-70 %).
 - **Mechanism:** One of the oxidative metabolites of Halothane (Trifluoro acetyl) acts like a HAPTEN that combines with the hepatocytes leading to formation of Hapten-protein complex $\rightarrow$ Antigen-Antibody reaction. (The antibody was isolated in those who developed jaundice after exposure to Halothane).
- ▶ **Recommendations of safety:**
 - Accurate anesthesia history: previous exposure and previous reaction to Halothane.
 - Exposure to Halothane within 3 month period should be avoided.
 - History of jaundice or pyrexia after previous exposure to Halothane is an absolute contraindication for its future use.

B) Nephrotoxicity:

- ▶ It occurs especially with Methoxyflurane, Enflurane, Isoflurane and Sevoflurane.
- ▶ **Theories of nephrotoxicity include:**
 - a. **Traditional Fluoride hypothesis:**
 - It depends on **LIVER metabolism** of anesthetics → producing inorganic fluoride which leads to renal dysfunction (according to the level of fluoride the renal dysfunction varies from clinical to subclinical).
 - This hypothesis is suitable for **Methoxyflurane** toxicity as it's very soluble so it continues to be metabolized with production of fluoride.
 - b. **Modified Fluoride hypothesis:**
 - It depends on **DURATION** of elevated fluoride level in plasma not only the concentration of fluoride.
 - This hypothesis is suitable more for **Enflurane** as the prolonged anesthesia with Enflurane is followed by renal dysfunction; however prolonged anesthesia with Isoflurane or Sevoflurane doesn't produce renal dysfunction.
 - c. **Renal anesthetic metabolism hypothesis:**
 - It depends on **INTRA-RENAL** metabolism of anesthetics to fluoride or any other toxic substances (this occurs by the effect of cytochrome P450 enzymes).
 - This is the most accepted theory.

C) Interactions between CO₂ absorbent and Volatile anesthetics:

1. Haloalkene Nephrotoxicity.
 2. Carbon monoxide toxicity.
- For detailed discussion see physics.

REMARK:

ENFLURANE	DESFLURANE
▶ Physical properties: ▪ MAC: 1.68% ▪ Blood/Gas coefficient: 1.9 ▶ Onset: Rapid induction & Recovery due to low solubility coef. & pleasant odor. ▶ CNS actions: As Halothane except on EEG: at high & moderate conc. there is epileptiform paroxysmal activities with twitching of face & arm muscles (it's contraindicated in epileptic pts). ▶ CVS actions: As Halothane but there is no central vagal stimulation so there is reflex tachycardia with hypotension + less arrhythmia. ▶ Respiratory actions: As Halothane but there is more resp. depression. ▶ Neuromuscular actions: As Halothane but there is more relaxation ▶ Hepatorenal action: As Halothane ▶ GIT action: ↓ GIT motility. ▶ Uterine action: Dose dependent uterine relaxation. ▶ Drug interaction: Potentiates NMB. ▶ CONTRAINDICATIONS: 1. Renal impairment 2. Intracranial mass. 3. Epileptic patients. 4. Malignant hyperthermia.	▶ Physical properties: ▪ MAC: 6-9 (7.3)% ▪ Blood/Gas coefficient: 0.49 ▶ Onset: the most rapid induction & recovery (but of limited use due to its pungent odor) due to its lowest solubility coef. ▶ CNS actions: As Halothane ▶ CVS actions: As Isoflurane but there is slight effect on ABP & HR + less coronary VD ▶ Respiratory actions: As Isoflurane ▶ Neuromuscular actions: As Halothane but there is more relaxation ▶ Hepatorenal action: As Halothane ▶ Drug interaction: Potentiates NMB. ▶ CONTRAINDICATIONS: 1. Intracranial mass. 2. Hypovolemic patients. 3. Malignant hyperthermia.

NITROUS OXIDE

Physical properties:

- Sweet smelling, non irritant, colorless, nonflammable.
- MW 44.
- Boiling point -88°C .
- Critical temperature 36°C , critical pressure 72.6 bars.
- Blood/gas solubility coefficient is 0.47 at 37°C

Pharmacokinetics:

A) MAC: (105%)

- So it is a weak anesthetic but good analgesic.
- MAC value is calculated theoretically from its oil/water solubility coefficient 3.2 & is confirmed clinically in volunteers anesthetized at pressure 2 ata, MAC was 52.5%

B) As It is weak anesthetic usually is combined with other agents:

The minimum FiO_2 to be administered is 30% (so N_2O can be administered is 70%), So N_2O alone is not sufficient to produce adequate depth of anesthesia, so it is usually used with another agent to avoid awareness.

C) The concentration effect:

- a) The higher the inspired concentration, the faster the rate of equilibrium between alveolar & inspired concentrations (see page 13).
- b) N_2O solubility in blood is $> \text{N}_2$ solubility
So the volume of N_2O entering the pulmonary capillary blood from the alveolus $>$ the volume of N_2 moving in the opposite direction $\rightarrow$ total volume of gas in the alveolus decreases, so the fractional concentration of the remaining gas increases leading to:
At high inspired concentrations of $\text{N}_2\text{O} \rightarrow$ the decrease in alveolar gas volume causes an increase in PaCO_2 .

D) The 2nd gas effect

When N_2O is inspired at high concentration with another agent (e.g. halothane). The reduction in the gas volume in the alveoli caused by absorption of $\text{N}_2\text{O} \rightarrow \uparrow$ the conc. of Halothane in the alveolus $\rightarrow \uparrow$ rate of equilibrium with the inspired gas.

Pharmacodynamics:

► Actions:

A) Actions on CNS:

- **Cerebral blood flow (CBF):** Increased with increased Cerebral O_2 consumption.
- **Intracranial Pressure (ICP):** Mildly increased due to increased blood volume due to increased CBF.
- **Analgesia** at levels below MAC.

B) Actions on CVS:

- Although N_2O is a direct myocardial depressant in vitro, the **COP, Heart rate & ABP** are unchanged or slightly increased in vivo.
- **Myocardial depressive** effect may be unmasked in pts with IHD or hypovolemia.
- **Rt. Ventricular End Diastolic Pressure** is increased due to constriction of pulmonary vessels.
- There is high incidence of Adrenaline induced **Arrhythmia** as it increases endogenous catecholamines.

C) Actions on Respiration:

- Increases **Respiratory rate** & Decreases **Tidal volume** (due to CNS stimulation and activation of peripheral pulmonary stretch receptors).
- Marked depression of **Ventilatory response** to Hypoxia.

D) Actions on Skeletal Muscles:

- Doesn't produce significant Muscle relaxation as other inhalational anesthetics; however it produces Muscle rigidity at high conc. in hyperbaric chambers.
- Doesn't trigger malignant hyperthermia.

E) Actions on GIT:

Postoperative nausea & vomiting (due to stimulation of CTZ & Vomiting centre).

F) Actions on Kidney:

Decreases **RBF, GFR, UOP**.

G) Actions on Liver:

Decreases **Hepatic blood flow**.

► Side effects:**A) Diffusion hypoxia:**

- It is the opposite of concentration effect.
- It occurs at the end of anesthesia when the inspired gas mixture is changed from N_2O/O_2 to N_2/O_2 the volume of N_2O diffusing from venous blood into alveolus > the volume of N_2 diffusing from alveolus to pulmonary capillary blood → the volume of gas in the alveoli is increased → gases in the alveoli are diluted → decreased PaO_2 & $PaCO_2$
- Diffusion hypoxia is transient in healthy individuals (lasts for 10 minutes) so administration of O_2 during this period is advisable.

B) Effect on closed gas spaces:

When blood containing N_2O equilibrates with a closed air containing cavity inside the body → the volume of N_2O diffusing inside the cavity > the volume of N_2 diffusing out.

a) In complaint spaces (e.g. bowel lumen, pleural, and peritoneal cavities): **The volume of the space increases**

- When administering N_2O at a concentration 75% → the volume of a cavity increases 3-4 times within 30 minutes.
- If an air embolus occurred in a patient who is receiving N_2O equilibrium with the gas bubble occurs → expansion of the embolus within seconds.

b) In spaces that can't expand (e.g. sinuses and middle ear): **The pressure is increased, so don't use N_2O in middle ear (tympanic membrane) surgery.****C) Systemic effects:**

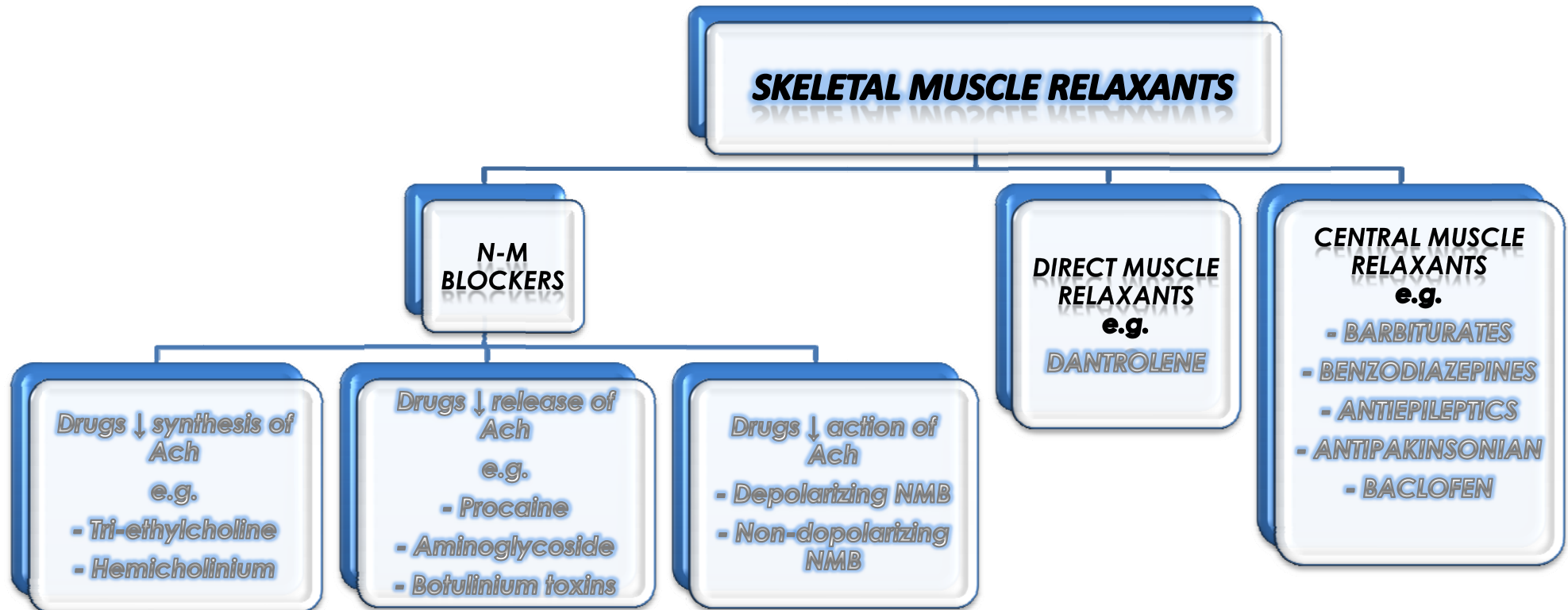
- Direct myocardial depression (masked by Sympathetic stimulation).
- Respiratory depression.
- Postoperative nausea and vomiting.

D) Toxicity:

- Depression of methionine synthetase → depression of vitamin B_{12} synthesis.
- Depression of Folic acid metabolism
- Depression of DNA synthesis (These effects are only important if duration of N_2O anesthesia is more than 8 hours).
- In Dentists: occupational exposure will lead to myelopathy with a picture similar to subacute combined degeneration of spinal cord.

E) Teratogenicity: There are possible teratogenic effects.**► Contraindications:**

1. Patients requiring high O_2 concentration.
2. Pulmonary hypertension.
3. Tympanic membrane grafting, intracranial air, intraocular air bubbles.
4. Pneumothorax, Pulmonary air cysts.
5. Acute intestinal obstruction.
6. Air embolism.
7. Should be avoided in pregnant pts due to possible teratogenicity.

CLASSIFICATION OF MUSCLE RELAXANTS

NEURO-MUSCULAR BLOCKING AGENTS

(Muscle Relaxants)

Classification:

A) Depolarizing Neuro-muscular Blockers:

- ✓ Suxamethonium chloride (Succinyl Choline).
- ✓ Decamethonium.

B) NON- Depolarizing Neuro-muscular Blockers:

1. According to **CHEMICAL NATURE:**

Benzyl isoquinolines	Amino-steroids
1. Tubocurarine.	1. Pancuronium.
2. Alcuronium.	2. Vecuronium.
3. Gallamine tri-ethiodide.	3. Pipecuronium.
4. Atracurium.	4. Rocuronium.
5. Cisatracurium.	5. Rapacurium.
6. Doxacurium.	
7. Mivacurium.	

2. According to **DUARTION OF ACTION:**

Long acting	Intermediate acting	Short acting	Short acting with Rapid onset
1. Pancuronium. 2. Pipecuronium. 3. Doxacurium.	1. Atracurium. 2. Cisatracurium. 3. Vecuronium. 4. Rocuronium.	Mivacurium.	Rapacurium.

SUCCINYL CHOLINE

(Suxamethonium chloride)

Chemical nature:

- It's Quaternary ammonium compound.
- It's also known as **Diacetylcholine** as it's composed of 2 joined Ach molecules, this structure is responsible for its mechanism of action, side effects and metabolism.

Pharmacokinetics:

A) Absorption: bypassed by the IV route.

B) Metabolism:

- a. IN PLASMA: it's metabolized rapidly by **Pseudocholinesterase** (plasma cholinesterase) into Succinylmonocholine, as the drug serum level drops Succinylcholine molecules diffuse away from neuromuscular junction → recovery.

Pseudocholinesterase enzyme is affected by:

1. Factors that decrease its synthesis: Liver diseases, Starvation, Pregnancy & Carcinomatosis.
2. Factors that decrease its activity: Hypothermia & Hypothyroidism.
3. Factors that Facilitates its removal: Plasmapheresis & Cardiopulmonary bypass.
4. Renal diseases
5. Drugs: see drug interactions.
6. INHERITED factors: see Sch apnea.

- b. IN PLASMA by nonspecific esterases.

- c. IN THE LIVER (very little).

C) Excretion:

Mainly by the kidney as water soluble inactive metabolites (10% is excreted unchanged in urine).

Indications: TRACHEAL intubation in:

1. Potentially full stomach patients to achieve rapid tracheal intubation (**RAPID SEQUENCE INDUCTION**).
2. Obstetric patients to achieve rapid tracheal intubation (**RAPID SEQUENCE INDUCTION**).
3. Suspected difficult tracheal intubation to reach optimal conditions for intubation.
4. Laryngeal spasm.

Dose: 1 - 1.5 mg/kg IV.

Pharmacodynamics:

- ▶ **Onset of action:** The most rapid muscle relaxant, it reaches 95% blockade **within 1 minute** (this rapid onset of action is mostly due to low lipid solubility).
- ▶ **Recovery from action:** Starts after **3 minutes** and become complete **within 12-15 minutes**.
- ▶ **Characteristics of Depolarizing neuromuscular blockade:**
 - Muscle fasciculation followed by relaxation (**Phase I block**).
 - Decreased response after application of **single twitch** to peripheral nerve.
 - Absence of fade after **Tetanic, Train-of-four & Double Burst** Stimulation.
 - Absence of **Post-tetanic potentiation**.
 - After continuous or repeated infusion **Phase II block** occurs, this carries the same characteristics of Non-depolarizing block (see side effects for more details).
- ▶ **Mechanism of action:** Each Nicotinic postsynaptic receptor in the neuromuscular junction consists of 5 glycoprotein subunits (2 α subunits, 1 β subunit, 1 δ subunit & 1 ϵ subunit).
After Sch Injection the quaternary ammonium radicals $N^+(CH_3)_3$ have the capacity to bind to each α subunit of Ach receptors → **alteration of the structural conformation of the receptors** → opening of ion channels for periods longer than Ach does, this results in initial **Depolarization** & muscle contractions (**FASCICULATION**) followed by muscle paralysis as **Repolarization** doesn't occur & further action potentials doesn't occur (this is called **Depolarizing** or **Phase I block**).
- ▶ **Side effects:** (2A, 5P, 1C, 2HYPER, 2M)

1) APNEA (Succinyl Apnea):

- **Definition:** It's prolongation of action (paralysis) of Sch Due to abnormal metabolism of Sch by Pseudocholinesterase.
- **Etiology:** decreased metabolism of Sch due to **abnormal structure (INHERITED)** or **decreased activity (AQUIRED)** of Pseudocholinesterase.

A. INHERITED FACTORS (Qualitative deficiency):

- The Autosomal gene responsible for the normal Amino acid sequence is E_1^U .
- The most common atypical gene is E_1^A which may be heterozygous or homozygous according to which the duration of paralysis depends as the following:
Heterozygous form $E_1^U E_1^A$ of the atypical gene → 30 minutes duration of paralysis.
Homozygous form $E_1^A E_1^A$ of the atypical gene → over 2 hours duration of paralysis.
- Other atypical genes are identified as: Fluoride gene E_1^F and Silent gene E_1^S

B. AQUIRED FACTORS (Quantitative deficiency): The structure of the enzyme is normal but there is decreased activity or synthesis or increased removal of the enzyme (see pharmacokinetics).

The neuromuscular blockade is prolonged only for minutes.

▪ **Management:**

1. The patient should be kept anesthetized with continued mechanical ventilation until muscle function returns to normal.
2. Fresh frozen plasma (source of cholinesterase) should be given.

- 2) **ALLERGY:** Slight histamine release may occur following repeated exposure in some patients.
- 3) **PAIN (Muscle Pain):**
 - **Cause:** initial fasciculation.
 - **Site:** Diaphragm & between scapulae.
 - **Incidence:** More common in young fit patients, large muscle mass & patients who are ambulant soon.
 - **Relief:**
Not relieved by analgesics & May be relieved by precurarization (10 mg Gallamine or 25 mg Atracurium), however this may decrease the potency of Sch.
- 4) **PRESSURE (INTRA-CRANIAL PRESSURE):**
Sch may lead to slight increase in CBF and ICP in some patients also muscle fasciculation stimulate stretch receptors which increase cerebral activity. The increase in ICP can be attenuated by hyperventilation.
- 5) **PRESSURE (INTRA-OCULAR PRESSURE):**
 - **Is increased.**
 - **Cause:** due to initial contraction of extra-ocular muscles.
 - **NOT reduced by:** precurarization.
 - **Duration:** as long as the neuromuscular block.
 - The increase may be sufficient to cause expulsion of the vitreal content in Open eye injury however the protection of the airway against aspiration of gastric contents takes the priority in patients with full stomach in addition to eye injury.
- 6) **PRESSURE (INTRA-GASTRIC PRESSURE):**
 - Abdominal wall muscle fasciculation increases intragastric pressure.
 - This increase is not sufficient to produce regurgitation of gastric content unless there is incompetent lower esophageal sphincter e.g. Hiatus hernia.
- 7) **Phase II block (2ry or Dual block):**
May occur with repeated or continuous infusions and is characterized by tetanic or train-of-four fade, tachyphylaxis, partial or complete reversal with anti-cholinesterase. It occurs due to receptor desensitization due to prolonged muscle membrane depolarization.
- 8) **CARDIOVASCULAR:**
 - Sch has both Muscarinic & Nicotinic effects due to the resemblance with Ach.
 - The muscarinic effect leads to **SINUS BRADYCARDIA**.
 - **Incidence:** more common in
 1. Patients with high vagal tone (physically fit & children).
 2. Non-atropinized patients.
 3. Repeated doses of Sch.
 - **Prevention:** Atropine should be given especially if more than one dose of Sch is given.
- 9) **HYPERKALEMIA:**
 - **Cause:** may be due to initial fasciculation.
 - Serum K^+ is increased by 0.5 mmol/L.
- 10) **HYPERTHERMIA (MALIGNANT HYPERTHERMIA):**
 - **Definition:** it's a hypermetabolic disorder of skeletal muscles due to increased intracellular Ca^{++} released from Sarcoplasmic reticulum.
 - **Triggering factors:** Sch, volatile agents, N_2O .
 - **Manifested by:** sustained jaw rigidity, unexplained tachycardia, Increased $ETCO_2$ & Decreased SaO_2 , Hyperthermia may be a late sign, but when it occurs, core temperature can rise as much as $1^\circ C$ every 5 min.
 - **Treatment:** Check ABC, hyperventilate with 100% O_2 , stop triggering agent & DANTROLENE 1mg/kg is given IV (In addition to treatment of complications such as acidosis and hyperkalemia).

11) MUSCLE CONTRACTIONS:

Patients with myotonia may develop generalized myoclonus after administration of Sch.

12) MASSETER RIGIDITY:

Transiently increases muscle tone in the Masseter muscles. There may be some difficulty in opening the mouth because of incomplete relaxation of the jaw. (Marked increase in tone preventing laryngoscopy and may be a premonitory sign of malignant hyperthermia).

► Contraindications:1. Renal failure:

These patients have elevated serum K^+ so further administration of Sch leads to more elevation in $K^+ \rightarrow$ arrhythmia which may even cause cardiac arrest.

2. Burned patients:

Damaged and swollen muscle cells $\rightarrow$ exaggerated K^+ release with Sch administration.

3. Diseases of muscles and it's nerve supply:

As muscle dystrophies and paraplegia.

Proliferation of extra junctional receptors $\rightarrow$ exaggerated K^+ release with Sch administration $\rightarrow$ severe Hyperkalemia.

4. Malignant hyperthermia.5. Closed head injury.6. Widespread intra-abdominal infections and severe trauma: due to Hyperkalemia.7. History of Sch Apnea.**REMARKS:****Modes of stimulation that assess the degree of N-M blockade:**

- TWITCH:** A stimulus of short duration (0.1-0.2 milliseconds) is applied to a peripheral nerve before & after a dose of muscle relaxant (crude assessment of the effect of drug)
- TRAIN-OF-FOUR:** it's the most commonly used. 4 stimuli are delivered at a frequency of 2 Hz, and the ratio of the amplitude of the 4th to the 1st response in a train (T4:T1 ratio) estimates the degree of block. The 4 twitches of the TOF disappear in reverse order as the degree of blockade deepens. The 4th twitch of the TOF disappears when 75-80% of the receptors are occupied, the 3rd twitch disappears at 85% occupancy, the 2nd twitch disappears at 85-90% occupancy, and the 1st twitch disappears at 90-95% occupancy.
- TETANIC STIMULATION:** it consists of repetitive, high-frequency (50 Hz or greater) stimulation. Loss of contraction during tetanic stimulation, known as tetanic fade, is a sensitive indicator of residual neuromuscular blockade.
- POST-TETANIC POTENTIATION:** application of a 50-Hz stimulus for 5 seconds is followed in 3 seconds by repetitive single twitches at 1 Hz. The number of twitches observed is inversely related to the degree of blockade.
- DOUBLE BURST STIMULATION:** It appears to be more sensitive than TOF stimulation for detecting small degrees of residual neuromuscular blockade. DB involves the application of an initial burst of three 0.2-millisecond impulses at 50 Hz followed by an identical stimulation in 750 milliseconds. The magnitude of the responses to double burst is approximately three times greater than that of TOF stimulation, thus making it easier to assess degree of fade present.

Identification of patients with Qualitative deficiency of Pseudocholinesterase (KALOW-GENIST Method):

- Plasma sample is taken after several days from neuromuscular block.
- The sample is put in a water bath containing substrate as Benzoylcholine.
- Chemical reaction between Benzoylcholine & Pseudocholinesterase forming a substance with special wave length emission that can be detected by spectrophotometer.
- If Dibucaine is added to water bath the reaction is inhibited.
- The percentage of inhibition is expressed as Dibucaine No.
- Dibucaine No. in:
 - Candidates with normal Pseudocholinesterase: 77-83.
 - Heterozygous Candidates $E_1^uE_1^a$: 45-68.
 - Homozygous Candidates $E_1^aE_1^a$: < 30.
 - No reaction: Silent gene E_1^s .
- If Fluoride is added to the solution instead of Dibucaine $\rightarrow$ Fluoride gene E_1^F may be detected.

► Drug interactions:

1. Anti-cholinesterases:

- **Phase I block:** is **Potentiated** through increasing Ach concentration at the nerve terminal By inhibiting acetyl cholinesterase which intensifies depolarization and They also reduce the hydrolysis of Succinylcholine by inhibiting Pseudocholinesterase.
- **Phase II block:** reversal of action.

2. Non-Depolarizing blockers:

- **Phase I block:** is **antagonized** as these drugs occupy some Ach receptors except for Pancuronium which augments Succinylcholine blockade by inhibiting Pseudocholinesterase.
- **Phase II block:** is **Potentiated**.

3. Antibiotics: e.g. streptomycin, aminoglycoside, clindamycin & tetracycline **Potentiate** Sch action.

4. Antiarrhythmics: e.g. Quinidine, Ca⁺⁺ channel blockers **Potentiate** Sch action.

5. Inhalational anesthetics: **Potentiate** Sch action.

6. Local anesthetics: High doses **Potentiate** Sch action.

7. Mg sulfate: Doses used in treatment of preeclampsia & eclampsia **Potentiate** Sch action.

8. Lithium carbonate: Prolong onset and duration of Sch.

NON- DEPOLARIZING N-M BLOCKERS

Chemical nature:

- Chemically they are of 2 types:
 1. Benzyl isoquinolines.
 2. Amino-steroids.
- All these drugs possess at least one quaternary ammonium compound group N⁺(CH₃)₃ to bind to α subunit of the post-synaptic nicotinic receptor.
- According to chemical structure these compounds have unique characteristics, For example, Amino-steroid compounds tend to be vagolytic, while Benzyl isoquinolines tend to release histamine.

Pharmacokinetics:

A) Absorption: bypassed by the IV route.

B) Metabolism:

- No metabolism occurs at the neuromuscular junction. By the end of surgery the drug diffuses along the concentration gradient passes into the plasma where it is cleared leading to more receptors become free to be occupied by Ach allowing recovery from block.
- An anti choline esterase is given at this time to increase the half life of Ach facilitating recovery.
- **Aminosteroids** (e.g., Pancuronium, Vecuronium, Pipecuronium, and Rocuronium) are deacetylated in the liver, and their action may be prolonged in the presence of hepatic dysfunction.
- **Atracurium** is unique in that it undergoes spontaneous breakdown at physiologic temperatures and pH (Hoffmann degradation) as well as ester hydrolysis.
- **Mivacurium** is like Sch as it's metabolized by Pseudocholinesterase.

C) Distribution: They are highly ionized & highly water soluble, which are distributed in plasma and Extracellular fluid, thus they have small volume of distribution.

D) Excretion:

- Unchanged in urine.
- **Vecuronium** and **Rocuronium** also have significant biliary excretion, and their action may be prolonged with extra hepatic biliary obstruction.

Dose:

- ▶ Usually administered in multiples of ED required to produce 95% neuromuscular block.
- ▶ At least a dose of 2 x ED₉₅ is required to produce adequate conditions for reliable tracheal intubation.

Pharmacodynamics:**▶ Characteristics of NON-Depolarizing neuromuscular blockade:**

- There is no muscle fasciculation.
- Decreased response after application of **single twitch** to peripheral nerve.
- Fade appears after **Tetanic, Train-of-four & Double Burst** Stimulation.
- **Post-tetanic potentiation** is present.
- Administration of Anti-cholinesterase → reversal of block.

▶ Mechanism of action:

- Unlike Sch they don't alter the structure conformity of post synaptic Ach receptors. Instead they compete with the neurotransmitter at this site i.e. they reversibly bind to 1 or 2 of α subunits of nicotinic receptors (whenever they are not occupied by Ach). The endplate potential produced doesn't reach the threshold necessary to fire off a propagating action potential to produce muscle contraction.
- Over 75% of post synaptic receptors have to be blocked in this way before there is failure of contraction.

▶ Factors affecting the duration of action of Non-depol. NMB:**1) AGE:**

- **Neonates:** In healthy neonates → there is higher ECV than adults so **resistance** may occur, while in sick or immature neonates → there is underdevelopment of N-M junction & other organs so **resistance** may occur.
- **Old:** impaired organ function → Impaired drug metabolism & excretion → **potentiation** of block.
- **Child:** relative **resistance** if drug was given on weight basis.

2) ACID-BASE BALANCE:

Metabolic (and to a lesser extent respiratory) acidosis **potentiates** and **prolongs** the block.

3) BODY TEMPERATURE:

Hypothermia impaired organ function → Impaired drug metabolism & excretion → **potentiation** of block.

4) CONCURRENT DISEASES:

Myasthenia gravis, renal, & hepatic patients are more **susceptible to action** of N-M blockers

5) DRUG INTERACTIONS

- Anti-cholinesterases:** Reversal of block.
- Depolarizing N-M blockers:** **Potentiate** non depolarizing N-M blockers action.
- Antibiotics:** e.g. streptomycin, aminoglycoside, clindamycin & tetracycline **Potentiate** non depolarizing N-M blockers action.
- Antiarrhythmics:** e.g. Quinidine, Ca^{++} channel blockers **Potentiate** non depolarizing N-M blockers action.
- Anticonvulsant:** e.g. Phenytoin, Carbamazepine & Na valproate increase resistance to N-M blockers action.
- Inhalational anesthetics** (mainly Isoflurane and Enflurane): **Potentiate** non depolarizing N-M blockers action.
- Local anesthetics:** High doses **Potentiate** non depolarizing N-M blockers action.
- Mg sulfate:** Doses used in treatment of preeclampsia & eclampsia **Potentiate** N-M blockers action.
- Loop diuretics:** **Potentiate** N-M blockers action.

6) ELECTROLYTE CHANGES:

Hypokalemia and hypocalcaemia potentiate and prolong the duration of N-M blockers.

▶ The rest will be discussed in table form.

	BENZYL ISOQUINOLINES				AMINO-STERIODS				
	Atracurium	Cisatracurium	Doxacurium	Mivacurium	Pancuronium	Pipecuronium	Vecuronium	Rocuronium	Rapacuronium
Onset (to reach 95% block)	2-3 minutes (Moderate)	2-3 minutes (Moderate)	4-6 minutes (Slow)	2-3 minutes (Moderate)	2-3 minutes (Moderate)	2-3 minutes (Moderate)	2-3 minutes (Moderate)	60-90 SEC. (Rapid)	60 SEC. (Most Rapid)
Duration (after intubation dose)	20-30 minutes (intermediate)	45-60 minutes (intermediate)	120-150 min. (Long)	10-20 minutes (short)	60-90 min. (Long)	60-90 min. (Long)	45-60 minutes (intermediate)	45-60 minutes (intermediate)	10-20 minutes (short)
Dose									
★ Intubation:	0.5 mg/kg.	0.1 mg/kg	0.05 mg/kg	0.15 mg/kg	0.1 mg/kg	0.1 mg/kg	0.1 mg/kg	0.5-0.9 mg/kg	1.5 mg/kg
★ Maintenance:	0.1 mg/kg/20-30 min.		0.005 mg/kg/20-40 min.		0.01 mg/Kg/30-45 min.		0.01 mg/Kg/15-20 min.		
★ Infusion:	5-10 µg/kg/min.	1-2 µg/kg/min.		5-10 µg/kg/min.			1-2 µg/kg/min.	5-10 µg/kg/min.	
Metabolism & Excretion	▪ Hoffman degradation 45%: spontaneous non enzymatic breakdown occurs at physiologic pH and temperature so it's can be used safely in hepatic & renal pts. ▪ Ester hydrolysis 45% ▪ 10% excreted unchanged	Hoffman degradation: mainly, Being 4 time more potent than Atracurium so it's given in lower doses so there is less Laudanosine production.	▪ Kidney: mainly > 90% ▪ Pseudo cholinesterase : 6%	▪ Pseudo cholinesterase at rate 88% of S.C, if normal cholinesterase → fast recovery (no need for anti-choline esterase), if reduced cholinesterase → prolonged action. ▪ Kidney: < 5%. ▪ Minimal % by true cholinesterase	▪ Kidney: 60-85% ▪ Liver: 30% → some active metabolites which are excreted by kidney. ▪ Bile excretion 10%	▪ Kidney: 60-90% ▪ Liver: 20% ▪ Bile excretion 20%	▪ Kidney: 25-40% ▪ Liver: 5% ▪ Bile excretion 70% (mainly) (The dose should be reduced in biliary obstruction and in liver diseases as it's associated with biliary stasis)	▪ Kidney: 40% ▪ Liver: insignific. ▪ Bile excretion 60% (mainly)	▪ Kidney: (mainly) ▪ Liver: insignific.
Side effects									
★ Histamine	Histamine release leading to local wheals & flare at site of injection	NO	NO	As Atracurium	NO	NO	As Atracurium	NO	As Atracurium
★ CNS	Laudanosine toxicity: a metabolite of Hoffman degradation that has epileptogenic properties in animals but not reported in humans and need high doses to occur)		NO	NO					

	BENZYL ISOQUINOLINES				AMINO-STEROIDS				
	Atracurium	Cisatracurium	Doxacurium	Mivacurium	Pancuronium	Pipecuronium	Vecuronium	Rocuronium	Rapacuronium
★ CVS	Hypotension & Tachycardia due to histamine release	NO	NO	As Atracurium	Hypertension and Tachycardia (due to it's vagolytic & slight Sympathomimetic effects)	NO	As Atracurium	NO	
★ Respiratory	Bronchospasm may occur esp. in asthmatic pts due to histamine release	NO	NO	As Atracurium		NO	As Atracurium	NO	As Atracurium but the bronchospasm is sever.
★ Others	Precipitates as free acid if mixed in the venous line with alkaline solution e.g. Thiopentone.	As Atracurium			augments SC blockade by inhibiting Pseudocholinesterase				

Remark: Rocuronium: Can be given Intramuscular (1 mg/kg for infants & 2 mg/kg for children), this provides adequate vocal cord and diaphragmatic paralysis for intubation, but not until after 3–6 min (deltoid injection has a faster onset than quadriceps), and can be reversed after about 1 hour.

ANTI-CHOLINESTERASE will be discussed in chapter 6.

ANALGESICS

Classification:

- ▶ Opioids e.g. Morphine
- ▶ Non steroidal anti-inflammatory drugs (NSAID) as Ketorolac (will be discussed in chapter 6).

OPIOIDS

Classification:

A) Pure Opioid agonist:

1. Natural opium alkaloids:
 - Phenanthrenes: Morphine, Codeine and Thebaine.
 - Benzylisoquinolines: Papaverine and Noscapine.
2. Semi-synthetic opium alkaloids: Dia-morphine (Heroin).
3. Synthetic opioids:

▪ Pethidine (Meperidine). ▪ Alfentanil. ▪ Remifentanil.	▪ Fentanyl. ▪ Sufentanil. ▪ Tramadol.
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B) Partial Opioid agonist: Buprenorphine.

At low doses they antagonize pure opioid induced analgesia, and at high doses they produce analgesia with ceiling (plateau) effect whatever the dose is.

C) Opioid agonist antagonist:

They have an agonist effect at one receptor (Kappa) and an antagonist effect on another receptor (Mu).

- | | |
|---|---|
| <ul style="list-style-type: none"> ▪ Nalbuphine (Nalufin) ▪ Levallorphan. ▪ Butorphenol. | <ul style="list-style-type: none"> ▪ Pentazocine. ▪ Nalorphine. |
|---|---|

D) Opioid antagonist:

Competitive antagonists at opioid receptors. The affinity for μ receptors appears to be much greater than for δ or κ receptors

- Naloxone (Narcan).
- Naltrexone.

Pharmacokinetics:

A) Absorption*:

- ▶ Bypassed by IV route.
- ▶ **Morphine** and **Pethidine**: Rapid and complete absorption follows the IM route with peak plasma levels usually reached after 20–60 min.

B) Distribution*:

- ▶ **Distribution & uptake**, which also affects onset and duration of opioids, depend on **Non-ionized fraction**, **Lipid solubility** and **Protein binding** of the drug e.g.
 - i. The low **fat solubility** of **Morphine** slows passage across the BBB → onset of action is slow and its duration of action is prolonged. While the high lipid solubility of **Fentanyl** and **Sufentanil** → rapid onset and short duration of action.
 - ii. **Alfentanil** has a more rapid onset of action and shorter duration of action than Fentanyl following a bolus injection, in spite of its lower lipid soluble than Fentanyl. While the high **non-ionized fraction** of Alfentanil at physiological pH and its small (V_d) volume of distribution increase the amount of drug available for binding in the brain.
- ▶ The distribution half-lives of all of the opioids are fairly rapid (5–20 min).
- ▶ **Redistribution** (see remark in page 2) terminates the action of small doses of all of these drugs, whereas larger doses depend on **Metabolism**.

Remarks:

- o **Fentanyl lollipop:** it represents **Oral transmucosal** absorption of Fentanyl which is an effective method of analgesia and sedation with rapid onset (10 min), in children (15–20 µg/kg) and adults (200–800 µg).
- o **Fentanyl patch:** due to low molecular weight and high lipid solubility of Fentanyl, it allows **transdermal absorption**:
 - The patch is constructed as a high-dose (10 mg) reservoir with a microporous membrane.
 - The large amount of Fentanyl in the reservoir provides a gradient for diffusion.
 - It takes approximately 8-12 hours to reach a steady state after the placement of the patch on the skin & it's usually changed every 72 hours.
 - This can be an effective alternative analgesic for chronic pain, when oral dosing is no longer an option.
- o **1st Pass effect:** Significant amounts of lipid-soluble opioids can be retained by the lungs (first-pass uptake) then diffuse back into the systemic circulation (where it becomes available for LIVER metabolism). The amount of pulmonary uptake depends on prior accumulation of another drug (decreases), a history of tobacco use (increases), and coincident inhalation anesthetic administration (decreases) **this phenomenon contributes to recovery from drug action.**
- o **Physical properties affecting distribution and uptake of opioids:**

AGENT	Non-ionized fraction	Lipid solubility	Protein binding
▪ Morphine	++	+	++
▪ Pethidine	+	+	+++
▪ Fentanyl	+	++++	+++
▪ Alfentanil	++++	+++	++++
▪ Sufentanil	++	++++	++++
▪ Remifentanyl	+++	++	+++

+ = Very low, ++ = Low, +++ = High, ++++ = Very high.

C) Metabolism:

Metabolism of most opioids occurs in the **LIVER**.

- ▶ **Alfentanil:** The small V_d is responsible for a short elimination half-life (1.5 h).
- ▶ **Morphine:** undergoes conjugation with glucuronic acid to form morphine 3-glucuronide and morphine 6-glucuronide.
- ▶ **Pethidine:** is N-demethylated to normeperidine, an active metabolite associated with seizure activity not reversed by Naloxone.
- ▶ The end products of **Fentanyl**, **Sufentanil**, and **Alfentanil** are inactive.
- ▶ **Remifentanyl:** has unique ester structure (which is an ultra short-acting opioid with a terminal elimination half-life less than 10 min) makes it susceptible to rapid ester hydrolysis by nonspecific esterases in blood and tissue.
 - The Metabolism is so rapid and so complete that the duration of infusion has **little effect on wake-up time** without **drug accumulation** following repeated boluses or prolonged infusions which differs from other currently available opioids.
 - Due to its extra hepatic hydrolysis it's suitable for patients with **hepatic dysfunction**.
 - Patients with Pseudocholinesterase deficiency have a normal response to Remifentanyl.

D) Excretion:

Excretion of most opioids occurs through **KIDNEYS**.

- ▶ **Morphine:** Renal failure prolongs its duration of action. The accumulation of morphine metabolites (morphine 3-glucuronide and morphine 6-glucuronide) in these patients has been associated with narcosis and ventilatory depression lasting several days as morphine 6-glucuronide is a more potent and longer-lasting opioid agonist than morphine.
- ▶ **Pethidine:** Renal failure ↑ the chance of toxic effects (seizure activity) of normeperidine accumulation.
- ▶ **Fentanyl**, **Sufentanil**, **Alfentanil** and **Remifentanyl** metabolites are excreted in urine and to lesser extent through bile.

Pharmacodynamics:

► Mechanism of action:

- **IN GENERAL:** Opiate–receptor activation **INHIBITS** the **presynaptic release** and **postsynaptic** response to **excitatory neurotransmitters** (e.g. acetylcholine, substance P) from **NOCICEPTIVE** neurons.
- **IN BRAIN:** Stimulation of **Periaqueductal gray Area** → stimulation of **Raphe Magnus Nucleus** → release of 5-HT & Enkephalins at **Substantia Gelatinosa of Rolandi** in the spinal cord → interruption of pain transmission.
- **IN SPINAL CORD:** Transmission of pain impulses can be interrupted at the level of the dorsal horn directly due to release of Noradrenalin from **Locus Caeruleus** which inhibits dorsal horn.
- The cellular mechanism for these neuromodulations may involve **alterations** in K^+ and Ca^{++} ion conductance.

► Types of Opiate receptors:

Although opioids exert their greatest effect within the central nervous system, opiate receptors have also been isolated from somatic and sympathetic peripheral nerves.

1. Mu (μ):

- **Morphine** is the prototype exogenous ligand.
- **Subtypes:**
 - **Mu₁:** Responsible for **ANALGESIA**, the endogenous ligands are **Enkephalins**.
 - **Mu₂:** Responsible for **RESPIRATORY DEPRESSION, BRADYCARDIA, PHYSICAL DEPENDENCE, EUPHORIA** and **ILEUS**. No endogenous ligands have been identified.

2. Delta (δ):

- It has the highest selectivity for the endogenous **Enkephalins**, but opioids still bind.
- Responsible for **modulation of activity** at **Mu** receptor. It is thought that **Mu** and **Delta** receptors exist together as a complex.

3. Kappa (κ):

- **Ketocyclazocine** and **Dynorphin** are the prototype exogenous and endogenous ligands, respectively.
- Responsible for **ANALGESIA, SEDATION, DYSPHORIA, PSYCHOMIMETIC effects, inhibits release of VASOPRESSIN** and **promotes DIURESIS**. Pure **Kappa** agonists do not produce respiratory depression.

4. Sigma (σ):

- **N-Allylnormetazocine** is the prototype exogenous ligand. This receptor is not a pure opiate-binding site; many other types of compounds bind at the sigma receptor.
- Responsible for **DYSPHORIA, HYPERTONIA, TACHYCARDIA, TACHYPNEA**, and **MYDRIASIS**.

Compound	R E C E P T O R S			
	Mu (μ)	Delta (δ)	Kappa (κ)	Sigma (σ)
Morphine	Agonist	Agonist	Agonist	-
Pethidine	Agonist	-	-	-
Fentanyl	Agonist	-	-	-
Sufentanil	Agonist	-	-	-
Buprenorphine	Partial Agonist	-	Antagonist	-
Butorphenol	Antagonist	-	Agonist	-
Pentazocine	Antagonist	-	Agonist	Agonist
Nalbuphine	Antagonist	Agonist	Agonist	Agonist
Nalorphine	Antagonist	Agonist	-	-
Naloxone	Antagonist	Antagonist	Antagonist	-
Naltrexone	Antagonist	-	-	-

2. **Smooth muscles:** increased smooth muscle tone → contraction of sphincter of Oddi (that will aggravate biliary colic), Ureters, Urinary bladder sphincter (that will lead to urine retention & aggravate renal colic).

G) Actions on Endocrinal system:

Block the release of hormones of stress response including catecholamines, ADH and cortisol.

H) Actions on Pregnancy:

- It relaxes Uterine muscles leading to **prolonged labor** and may be delayed labor.
- It crosses the placental barrier during labor leading to **Neonatal respiratory depression**.
- Neonates of chronic users show **withdrawal symptoms**.

I) Actions on Eye:

Miosis due to stimulation of Edinger-Westphal nucleus of Oculomotor nerve.

J) Post-operative nausea & vomiting: The MOST COMMON postoperative complaint

Due to:

- i. Stimulation of CTZ.
- ii. Dopamine like action (so anti-dopaminergic receptors are effective in controlling postoperative nausea & vomiting).
- iii. Vestibular components, so ambulant pts suffer more.

K) Histamine release: leading to:

- Local wheel and pruritis at site of injection.
- Hypotension. (due to VD)
- Bronchospasm.

► **Contraindications:**

1. Hepatic or Renal dysfunction.
2. Epileptic patients.
3. Cases with ↑ ICP as head trauma.
4. Hypovolemic patients as it'll unmask the hypotensive effect.
5. Pulmonary diseases as COPD, Cor pulmonale.
6. Biliary & renal colic.
7. Premedication in cholecystectomy.
8. Prostatic hypertrophy.

The rest of OPIOIDS will be discussed in table form.

	PETHIDINE	FENTANYL	ALFENTNYL	SUFENTANYL	REMIFENTANYL
Onset of action	Rapid onset more than morphine	Very rapid onset (within 1-2 minutes).	Very rapid onset	Very rapid onset more than Fentanyl.	Very rapid onset more than Fentanyl.
Duration of action	2-3 hours	20-30 min. after single IV bolus (due to redistribution). 2-5 hrs after large dose or IV infusion (due to elimination).	5-10 min. so it's used as IV infusion.	Shorter than Fentanyl.	Ultra-short acting due to metabolism.
Routes of administration & Dosage	1. IV: 0.5-5 mg/kg. 2. IM: 1 mg/kg. 3. Epidural: The same as IV route. 4. Intrathecal: $\frac{1}{10}$ of the IV route.	1. IV: 1-2 $\mu\text{g/kg}$ for intra-operative analgesia, for major surgery can be increased to 150 $\mu\text{g/kg}$ (this large dose needs post-operative ventilation for 24 hrs). 2. Epidural: The same as IV route. 3. Intrathecal: $\frac{1}{10}$ of the IV route. 4. Trans-dermal and oral trans-mucosal routes (see page 31). 5. Intranasal: used as premedication in children, its onset is within 5 min.	IV: 5 $\mu\text{g/kg}$ for intra-operative analgesia, for major surgery loading dose 100 $\mu\text{g/kg}$ is given followed by 0.5-3 $\mu\text{g/kg/min}$ IV infusion (this large dose needs post-operative ventilation).	IV: 0.05 $\mu\text{g/kg}$ for intra-operative analgesia, for major surgery can be increased to 30 $\mu\text{g/kg}$ (this large dose needs post-operative ventilation).	IV: loading dose 1 $\mu\text{g/kg}$ is given followed by 0.5-20 $\mu\text{g/kg/min}$ IV infusion.
Actions					
A) Potency	$\frac{1}{10}$ potency of Morphine.	100 times as Morphine	20 times as Morphine.	600 times as Morphine.	100 times as Morphine.
B) Analgesia	As Morphine	As Morphine	As Fentanyl	As Fentanyl	As Morphine but preferred when rapid recovery is needed as in day case anesthesia and in neurosurgery.

	PETHIDINE	FENTANYL	ALFENTANYL	SUFENTANYL	REMIFENTANYL
C) CNS	As Morphine but less euphoria and convulsions is more common in toxic doses due to normeperidine.	Less than Morphine	As Fentanyl	As Fentanyl	As Morphine but it doesn't produce loss of consciousness and there is no ↑ ICP & seizure activity.
D) CVS	▪ HR: increased due to Atropine-like action (as its structure is similar to Atropine). ▪ ABP: not affected except in hypovolemic pts due to peripheral VD. ▪ Arrhythmia: decreases incidence of Ventricular arrhythmia due to Quinidine-like action.	As Morphine	It inhibits CVS (HR & ABP) more than Fentanyl especially in elderly and critically ill pts.	As Fentanyl	Mild bradycardia.
E) Respiration	▪ No action on cough reflex. ▪ Inhibits RC to the same degree as Morphine in equipotent doses.	▪ Inhibits RC directly (<i>IV bolus may lead to delayed RC inhibition due to its sequestration in gastric juice and subsequent intestinal absorption</i>). ▪ Muscle rigidity: large IV doses may → generalize hypertonus of skeletal muscles which in its severe form may prevent ventilation. Benzodiazepine pretreatment may prevent it.	As Fentanyl	As Fentanyl	Dose related direct Inhibition of RC.
F) Smooth muscles	▪ Decreases GIT motility. ▪ Relaxes smooth muscles of GIT and urinary tract so it can be used in renal colic.	As Morphine	As Fentanyl	As Fentanyl	As Fentanyl
G) Endocrine	As Morphine	As Morphine	As Morphine	As Morphine	As Morphine

	PETHIDINE	FENTANYL	ALFENTNYL	SUFENTANYL	REMIFENTANYL
H) Pregnancy	▪ Doesn't prolong labor. ▪ It crosses the placental barrier during labor leading to Neonatal respiratory depression. ▪ Neonates of chronic users show withdrawal symptoms				
I) Eye	No Miosis.				
J) Post-operative nausea & vomiting	As Morphine	As Morphine	As Fentanyl	As Fentanyl	As Fentanyl
K) Histamine release	Less than Morphine	Less than Morphine	Less than Morphine	Less than Morphine	Less than Morphine
Contraindications	1. Hepatic or Renal dysfunction. 2. Epileptic patients. 3. Cases with ↑ ICP as head trauma. 4. Hypovolemic patients as it'll unmask the hypotensive effect. 5. Pulmonary diseases as COPD, Corpulmonale.	As Morphine	As Fentanyl	As Fentanyl	As Fentanyl but it can be used in neurosurgery pts.
Drug interactions	MAO inhibitors, L-dopa and Tyramine in food with opioids especially Pethidine → life threatening hypertensive crisis, hyper-reflexia, convulsions and coma.		After 7 days course of Erythromycin, it impairs Alfentanil metabolism leading to more sedation and more respiratory depression.		

MORPHINE

► **Onset of action:** Slow onset of action with peak effect 15-20 min. after IV or 60-90 min. after IM.

► **Duration of action:** long acting 3-4 hrs duration after IV or IM routes.

► **Routes of administration & Dosage:**

1. IV: 0.1 mg/kg up to 1 mg/kg.
2. IM: 0.2 mg/kg.
3. Oral: 0.4 mg/kg.
4. Epidural: the same as IV dose.
5. Intrathecal: $\frac{1}{10}$ of IV dose.
6. Rectal.

► **Actions:**

A) **Potency:** It's the **GOLDEN** standard against which all other opioids are judged.

B) **Analgesia:**

- **For:**
 - i. Somatic and visceral types of pain
 - ii. Dull, continuous and sharp pain.
 - **Mechanism:**
 - i. Peripheral anti-nociceptive action.
 - ii. Increase pain threshold.
 - iii. Increase psychological and emotional components of pain.
- It's augmented by euphoria, drowsiness with large doses.

C) **Actions on CNS:**

- **Sedation:** it progress to sleep and anesthetic state with large doses.
- **Euphoria, Hallucination and Dysphoria** i.e. mental discomfort, restlessness and malaise.
- **Cerebral metabolic ate:** reduce Cerebral O_2 consumption, CBF, and ICP, but less than Barbiturates or Benzodiazepines.
- **EEG changes:** is minimal, although high doses are associated with slow δ wave activity.
- May rarely cause **seizure activity**.

REMARK: there are some reports of mild and usually transient increases in CBF velocity and ICP following opioid boluses in patients with **brain tumors** or **head trauma**. Because opioids also tend to produce a mild decrease in mean ABP, the resulting fall in CPP may be significant in some patients with abnormal intracranial elastance.

D) **Actions on CVS:**

- **HR:** Vagus-mediated Bradycardia, The combination of Morphine with other anesthetic drugs (e.g. nitrous oxide, benzodiazepines, barbiturates, and volatile agents) can result in significant myocardial depression.
- **ABP:** often falls as a result of bradycardia, vasodilatation (due to inhibition of vasomotor centre & Histamine release), and decreased sympathetic reflexes.

E) **Actions on Respiration:**

- **Respiratory centre:** depressed (**Decreased RR & V_T**) with elevated **Apneic threshold** and decreased **hypoxic drive** (Resting $PaCO_2$ increases and the response to a CO_2 challenge is blunted, resulting in a shift of the CO_2 response curve downward and to the right which $\rightarrow$ cerebral VD $\rightarrow$ $\uparrow$ ICP).
- **Cough reflex** inhibition.

F) **Actions on Smooth muscles:**

1. **GIT:** Suppresses peristaltic movements leading to:
 - **Delayed gastric emptying** (which may induce vomiting).
 - **Constipation** in patients receiving long-term opioid therapy (e.g. for cancer pain) due to **DECREASED** perception of sensory stimuli of defecation & **INCREASED** tone of sphincter.

REMRK:**TRAMADOL (Tramal)**

- **Mechanism of action:** Weak μ receptor agonist, and also exhibits an effect via noradrenergic and serotonergic pathways (catecholamine reuptake inhibition).
- **Potency:** $1/10$ potency of Morphine
- **Advantages:** used for both acute and chronic pain management & it appears to have much lower risk for tolerance and addiction.
- **Side effects:** sedation, drowsiness, dizziness, nausea, vomiting, dry mouth, postural hypotension & may lead to seizure activity.
- **Contraindications:** Liver & Kidney diseases and epileptic pts.
- **Dose:** Maximum dose is 600 mg in 24 h and can be increased to 1800 mg but with higher risk of convulsions.

NALBUPHINE (Nalufin) Agonist Antagonist but used as agonist

- **Onset:** 2-3 min after IV.
- **Dose:** 10-20mg.
- More potent than Morphine.

NALOXONE

Onset: within 1 min after IV route.

Duration: 20-30 min.

Clinical uses:

1. Low doses of Naloxone can reverse the **Ventilatory depression**, **Sedation** and **Loss Of Consciousness** produced by opioids, whatever the route of administration, but due to the short duration of action repeated doses or IV infusion are given (Some degree of opioid analgesia can often be spared if the dose of Naloxone is limited to the minimum required to maintain adequate ventilation).
2. Can be used in diagnosis of opioid dependence, withdrawal symptoms will appear.

Side effects:

Abrupt reversal of analgesia (large doses of Naloxone) may produce a catecholamine surge, resulting in tachycardia, hypertension, pulmonary edema, and cardiac arrhythmia.

Dose:

- **IV bolus:** 0.5-1 $\mu\text{g/kg}$ every 3–5 min until adequate ventilation and alertness, supplementary doses may be required after 20-30 min.
- **IV infusion:** 4-5 $\mu\text{g/kg/hr}$.
- **IM:** twice IV dose with longer duration of action.
- Neonatal respiratory depression resulting from maternal opioid administration is treated with 10 $\mu\text{g/kg}$, repeated in 2 min if necessary (neonates of opioid-dependent mothers will exhibit withdrawal symptoms if given Naloxone).

NALTREXONE: As Naloxone but given orally only.

NALORPHINE (Agonist Antagonist but used as antagonist only)

- **Agonist:** in absence of Morphine but not used as agonist as it $\rightarrow$ Anxiety, visual hallucinations.
- **Antagonist:** in the presence of Morphine (By competition for opiate receptors).
- **In Addicts:** leads to withdrawal symptoms.
- **Dose:** 5-10 mg IV, IM, SC, Intra-umbilical.
- **USES:** Neonatal asphyxia, Acute morphine poisoning, Diagnosis of addicts.

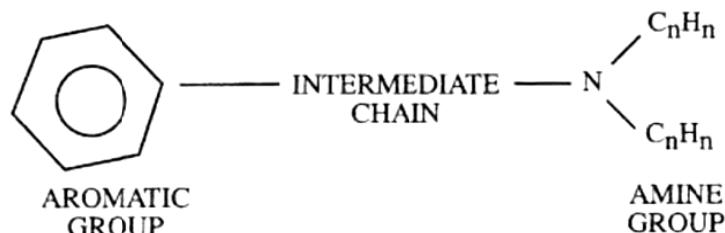
LEVALLORPHANE (Agonist Antagonist but used as antagonist only)

- The same as Nalorphine but more potent.
- **Dose:** 0.5 mg.

LOCAL ANESTHETICS

Classification:

1. **Aminoesters:** Esters are local anesthetics with an ester link between the aromatic and amine groups. Commonly used esters include Procaine, Chlorprocaine, Cocaine, and Tetracaine.
2. **Aminoamides:** Amides are local anesthetics with an amide link between the aromatic and amine groups. Commonly used amide anesthetics include Lidocaine, Bupivacaine, Mepivacaine, and Ropivacaine.



Structure–Activity Relationships

- ▶ Local anesthetics consist of a lipophilic group (usually aromatic group) separated from a hydrophilic group (usually amine group) by an intermediate chain that includes an ester or amide linkage.
 - ▶ Local anesthetics are weak bases that usually carry a positive charge at the tertiary amine group at physiological pH.
 - ▶ Physicochemical properties of local anesthetics depend on the nature of the aromatic ring, the intermediate chain, and the amine group.
1. **Potency**: is related to **Lipid solubility** which is responsible for ability of the drug to penetrate cell membrane, potency and lipid solubility increase by adding a halide to the aromatic ring, an ester linkage, and large alkyl groups on the tertiary amide nitrogen.
 2. **Onset of action**: depends on the **Degree of ionization** (pKa) i.e. relative concentration of the nonionized lipid-soluble form (B) and the ionized water-soluble form (BH⁺). Local anesthetics with a pKa closest to physiological pH will have a higher concentration of nonionized base that can pass through the nerve cell membrane, and with more rapid onset
 3. **Duration of action**: The greater the **Protein binding**, the longer the duration of action. The duration of action is also influenced by peripheral vascular effects of the local anesthetics. For example, Lidocaine, Prilocaine, and Mepivacaine provide anesthesia of similar duration in an isolated nerve. However, Lidocaine is a more potent vasodilator, increasing absorption and metabolism of the drug, thus resulting in a shorter clinical blockade than that produced by Prilocaine or Mepivacaine.
 4. Also alteration in **Molecular Structure** affects the **Potency** and **Duration of action** of LA e.g. adding a butyl group to Mepivacaine produces Bupivacaine which is longer acting and 4 times more potent.

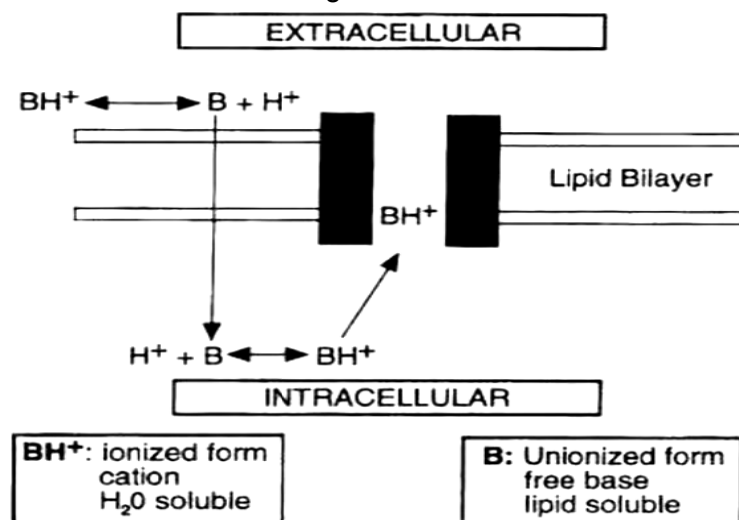
Mechanism of action:

- ▶ **Normal neuronal ACTION POTENTIAL:**
 - Neurons maintain a resting membrane potential (RMP) by active transport and passive diffusion of ions. **Na⁺-K⁺ ATPase pump** couples the transport of 3 Na⁺ ions out of the cell for every 2 K⁺ ions it moves into the cell.
 - The cell membrane is normally much more permeable to K⁺ than to Na⁺ → relative excess of negatively charged ions (anions) accumulates intracellularly. This accounts for the **negative resting potential difference** (−90 mV polarization).

- Neurons have membrane-bound, **voltage-gated Na^+ and K^+ channels** that produce membrane **Depolarization** following chemical, mechanical, or electrical stimuli generating an **ACTION POTENTIAL**.
- This is followed by increased intracellular positively charged ions $\rightarrow$ reversal of membrane potential to +40 mV. However, inactivation of voltage-gated Na^+ channels occurs along with a transient increase in K^+ conductance through voltage-gated K^+ channels (allowing more K^+ to exit the cell) which return the membrane to its resting potential.
- Baseline concentration gradients are reestablished by the **$\text{Na}^+ - \text{K}^+$ pump**.

► **After Local anesthetic injection:**

- Na^+ channels are membrane-bound proteins that are composed of one large α -subunit, through which Na^+ ions pass, and one or two smaller β -subunits. Voltage-gated Na^+ channels exist in three states **Resting**, **Activated (Open)**, and **Inactivated**.
- Most local anesthetics bind the α -subunit and block voltage-gated Na^+ channels from inside the cell, preventing subsequent channel activation and interfering with the large transient Na^+ influx associated with membrane **Depolarization**, with increasing concentrations of local anesthetic, impulse generation & conduction slows progressively until an **ACTION POTENTIAL** can't be generated and impulse propagation is abolished.
- Local anesthetics have a much greater affinity for the channel in the activated and inactivated state than in the resting state. As a result, local anesthetic action is both voltage and time dependent; their effect is greatest when nerve fibers are firing rapidly.
- Local anesthetics may also block Ca^+ and K^+ channels and N-methyl-D-aspartate (NMDA) receptors to varying degrees. Differences in these additional actions may be responsible for clinically observed differences between agents.



Pharmacokinetics:

A) Absorption:

- Most mucous membranes (e.g., ocular conjunctiva, tracheal mucosa) provide a weak barrier to local anesthetic penetration $\rightarrow$ rapid onset of action.
- While intact skin requires a high water concentration for its penetration and a high concentration of lipid-soluble local anesthetic base to ensure analgesia.
- Systemic absorption of LA is affected by:
 1. **Physiochemical properties** of the drug and the degree tissue binding.
 2. **Site of injection**: The rate of systemic absorption is proportionate to the vascularity of the site of injection (intravenous > tracheal > intercostal > caudal > paracervical > epidural > brachial plexus > sciatic > subcutaneous).
 3. **Use of vasoconstrictors**: The addition of Adrenaline or less commonly Phenylephrine causes vasoconstriction at the site of administration $\rightarrow$ decreased absorption $\rightarrow$ increases **neuronal uptake**, enhances the **quality of analgesia**, prolongs the **duration of action**, and limits **toxic side effects**. The effects of vasoconstrictors are more with shorter-acting agents. Adrenaline can also augment and prolong analgesia through activation of α_2 -adrenergic receptors.

B) Distribution:

Distribution depends on organ uptake, which is determined by the following factors

1. **Tissue Perfusion:** The highly perfused organs (brain, lung, liver, kidney, and heart) are responsible for the initial rapid uptake, which is followed by a slower redistribution to moderately perfused tissues (muscle and gut). In particular, the lung extracts significant amounts of local anesthetic → the threshold for systemic toxicity needs much lower doses following arterial injections than venous injections.
2. **Tissue/Blood Partition Coefficient:** Strong plasma protein binding tends to retain anesthetic in the blood decreasing its uptake, whereas high lipid solubility facilitates tissue uptake.
3. **Tissue Mass:** Muscle provides the greatest reservoir for local anesthetic agents because of its large mass.

C) Metabolism and Excretion:

The metabolism and excretion of local anesthetics differ depending on their structure:

1. Esters:

- **METABOLISM:** Ester local anesthetics are metabolized by Pseudocholinesterase (plasma cholinesterase) which is very rapid.
- **EXCRETION:** water-soluble metabolites are excreted in the urine.
- **TOXICITY:** Patients with genetically abnormal Pseudocholinesterase are at increased risk for toxic side effects, as metabolism is slower.
- **CSF lacks esterase enzymes**, so the termination of action of intrathecally injected ester LAs depends on their absorption into the bloodstream.

2. Amides:

- **METABOLISM:** Amide local anesthetics are metabolized by cytochrome P-450 enzymes in the liver (the rate of amide LAs metabolism varies according to each drug but overall is much slower than ester hydrolysis)
- **EXCRETION:** Very little drug is excreted unchanged by the kidneys, although the metabolites are dependent on renal clearance.
- **TOXICITY:** Decreased hepatic function (e.g., cirrhosis of the liver) or blood flow (e.g., congestive heart failure, Vasopressors, or H₂-receptor blockers) will reduce the metabolic rate and predispose patients to systemic toxicity.

Pharmacodynamics:

▶ **Mechanism of action:** See before.

▶ **Side effects:**

1. Systemic effects & TOXICITY:

- o Toxicity is often directly proportionate to potency.
- o Mixtures of local anesthetics should be considered to have roughly additive toxic effects.
- o **Causes:**
 - The most common cause is inadvertent intravascular injection.
 - Absolute overdose.
- o **Factors affecting toxicity:** (pharmacokinetics).
- o **The Effects:**

A) On CNS:

- **Early symptoms:** circumoral numbness, tongue paresthesia, and dizziness.
- **Sensory symptoms:** may include tinnitus and blurred vision.
- **Motor symptoms:** Muscle twitching followed by tonic-clonic seizures
- **Excitatory signs** (e.g. restlessness, agitation, nervousness,) often precede CNS depression (e.g. slurred speech, drowsiness, unconsciousness, RC depression).
- **Benzodiazepines** and **hyperventilation** raise the threshold of local anesthetic-induced seizures. **Thiopentone** (1-2 mg/kg) quickly terminates seizure activity + adequate ventilation and oxygenation.

B) On CVS:

- Direct cardiac muscle membrane changes:
 1. Depress myocardial **automaticity** and reduce the duration of the refractory period.
 2. Depress myocardial **contractility** and **conductivity** at higher concentrations.
- All local anesthetics except for cocaine produce smooth muscle relaxation → **arteriolar VD**.
- These effects → **bradycardia**, **heart block**, and **hypotension** may end in cardiac arrest.
- Major CVS toxicity requires about 3 times the concentration of blood that produces seizures, so cardiac arrhythmia or circulatory collapse is presenting sign of local anesthetic toxicity during general anesthesia, however transient CVS stimulation (tachycardia and hypertension) may occur earlier due to CNS excitation.

C) On Respiration:

- LAs **relax bronchial smooth muscle**.
- **Apnea** can result from phrenic and intercostal nerve paralysis or depression of RC.
- Intravenous **Lidocaine** (1.5 mg/kg) may be effective in blocking the reflex bronchoconstriction associated with intubation.
- **Lidocaine** depresses hypoxic drive (the ventilatory response to low PaO₂).

D) On Skeletal muscles:

- LAs are myotoxic, When directly injected into skeletal muscle, Bupivacaine > Lidocaine > Procaine (*Histologically, myofibril hyper-contraction progresses to lytic degeneration, edema, and necrosis*) and regeneration usually occurs after 3–4 weeks.
- Concomitant steroid or adrenaline injection worsens the myonecrosis.

E) On Blood:

- Lidocaine decreases coagulation (prevention of thrombosis and decreased platelet aggregation) and enhances fibrinolysis of whole blood.
- Large doses of Prilocaine can → met-hemoglobinemia.

REMARK (Met-hemoglobinemia & LAs)

- *Metabolites of Prilocaine (O-toluidine) accumulate after large doses of drug (> 10 mg/kg) & convert hemoglobin to met-hemoglobin.*
- *Benzocaine, a common ingredient in local anesthetic sprays, can also cause met-hemoglobinemia.*
- *Treatment of significant met-hemoglobinemia includes intravenous administration of Methylene blue (1–2 mg/kg of a 1% solution over 5 min). Methylene blue reduces met-hemoglobin (Fe³⁺) to hemoglobin (Fe²⁺).*

F) On Immunity:

- True hypersensitivity reactions to LAs are uncommon.
- **Esters** are more likely to induce an allergic reaction because they are derivatives of PABA, a known allergen.
- Commercial multidose preparations of **Amides** containing **methylparaben**, which is chemically similar to PABA, may lead to allergic reactions.

2. Complications of epidural and subarachnoid injection:A) Anterior spinal artery syndrome:

- Paresis and variable sensory deficit of lower extremities.
- It is more likely related to a vascular event rather than neurotoxicity from LAs.

B) Transient Radicular irritation:

- More common with Lidocaine than Bupivacaine and Tetracaine.
- More common if lithotomy position is used in surgery.
- Manifestations:
 - Pain: Moderate to severe.
 - Site: lower back, buttocks, and posterior thighs.
 - Onset: 24 hours after complete recovery from spinal anesthesia (Delayed onset due to time required for neural inflammatory reaction).
 - Duration: full recovery in 7 days.

C) Cauda equina syndrome:

- Diffuse injury of lumbosacral plexus manifested by:
Sensory: anesthesia.
Motor: Paraplegia.
Autonomic: Bowel and bladder sphincter dysfunction.
- Occurs with:
Large doses of L.A. reaching subarachnoid space due to:
 - 1) Continuous spinal anesthesia.
 - 2) Accidental subarachnoid injection of epidural dose.
 - 3) Repeated injection after failed spinal trials.
 Common with continuous spinal anesthesia via microcatheter with Lidocaine 5%.

3. Prevention of toxicity:**1. Avoidance of accidental intravascular injection by:**

- a) Careful aspiration tests should be done before injection.
- b) Injection of 2-3 ml of solutions containing Adrenaline, if there is increase in HR within 1-2 min → intravascular injection.
- c) The injection should be slow.
- d) The patient should be observed for early manifestations of toxicity.

2. Avoidance of overdose:

- a) Use the appropriate drug and dose for each block.
- b) Maximum safe dose should be considered.
- c) Concomitant use of other drugs may increase risk of overdose and toxicity e.g. H₂-blockers.

4. Treatment of toxicity: (Facilities for ttt should available at the same time and place of use of LAs)

1. Respiration: Airway maintenance + O₂ supply to facilitate ventilation.
2. Convulsions: **Benzodiazepines** and **hyperventilation** raise the threshold of seizures. **Thiopentone** (1-2 mg/kg) quickly terminates seizure activity.
3. CVS collapse: α and β agonists with proper intravascular hydration are given e.g. Ephedrine doses of 3-5 mg.

► **Clinical factors affecting drug profile:**

1. **Dose:** increasing the dose → faster onset and longer duration of action
this is done by: increasing concentration of the drug and/or increasing Volume.
(Large volume of diluted concentration is more effective than small volume of concentrated solution).
2. **Site of injection:** Affects the onset and duration of action. (Local infiltration > subarachnoid > peripheral nerve block > epidural > brachial plexus block).
3. **Pregnancy and age:** increase the segmental spread of the epidural block.
4. **Young, fit, tall, obese, alcoholic, and anxious** patients require higher doses.
5. **Mixtures:** combinations of LAs can be used to get the benefit of both drugs but care must be taken that toxic effects is additive.

► **Drug Interactions**

1. Local anesthetics potentiate **NMB**.
2. **Succinylcholine** and ester local anesthetics depend on Pseudocholinesterase for metabolism. Concurrent administration may potentiate the effects of both drugs.
3. **Pseudocholinesterase inhibitors** can lead to decreased metabolism of ester local anesthetics.
4. **Cimetidine** and **Propranolol** decrease hepatic blood flow and Lidocaine clearance. So higher Lidocaine blood levels increase the risk of systemic toxicity.
5. **Opioids** (e.g., Fentanyl, Morphine) and **α_2 -adrenergic agonists** (e.g., Adrenaline, Clonidine) potentiate local anesthetic pain relief.

Local Anesthetic Drugs: will be discussed in table form.

	ESTERS					AMIDES					
	Cocaine	Procaine	Chloro-procaine	Benzocaine	Amethocaine (Tetracaine)	Lignocaine	Mepivacaine	Bupivacaine	Ropivacaine	Prilocaine	Etidocaine
Maximum safe dose	3 mg/kg	12 mg/kg	12 mg/kg			4.5 mg/kg & 7 mg/kg with Adrenaline	As Lignocaine	3 mg/kg	8 mg/kg	8mg/kg	4 mg/kg
Relative duration (to Lignocaine)	0.5	0.75	0.75	2 (longer duration due to higher ptn binding)	Longer duration due to slow hydrolysis	1		2-4 (longer duration due to higher ptn binding)	2-4 (due to higher ptn binding & local VC effect)	1.5	
Toxicity	Very high	Low	Low	Low	high	Medium		Medium	Medium	low	high
Uses	No	No		Topical	- Topical. - Spinal.	- Infiltration. N. block. - Caudal. - Epidural. - Spinal. - Topical. - IVRA.		- Infiltration. N. block. - Caudal. - Epidural. - Spinal.	- Infiltration. N. block. - Caudal. - Epidural. - Spinal.	- Infiltration. N. block. - Caudal. - Epidural. - Spinal.	- Infiltration. N. block. - Caudal. - Epidural. - Spinal.
Other properties			- Used in USA. - Highly cleared by plasma esterases		- Met-hemoglobin - It's the standard drug in North America for sub-arachnoid anesthesia. - Very potent.	Used as anti-arrhythmic. (Class I B)		- More potent (due to high lipid solub.) & longer duration than Lignocaine - Toxicity: Less on CNS than Ligno But more Cardio-toxic than any other LA.	- Chemically derived from Bupivac. - Less CNS toxicity & cardio-toxic due to low lipid solub. - Produces dissociation between Motor & sensory blockade so it's drug of choice for epidural use in obstetrics & postop. Analgesia.	Met-hemoglobin	In contrast to other LAS it affects motor > sensory

IVRA: Intra Venous Regional Anesthesia

Local Anesthetic additives:

1) Vasoconstrictors (e.g. Adrenaline, Noradrenalin, Phenylephrine, Felypressin):

► **Advantages:**

1. Slows the rate of absorption → decreased systemic toxicity & Increased duration of action.
2. α_2 -adrenergic agonists (e.g., adrenaline, Clonidine) potentiate local anesthetic pain relief.

► **Disadvantage:**

Theoretically they increase risk of neurological deficits by rendering nerve tissues ischemic.

► **Contraindications:**

1. IHD.
 2. Cardiac arrhythmia.
 3. Hypertension.
 4. Peripheral nerve blocks to fingers, toes, and penis (areas with end arteries without collateral blood flow).
 5. IVRA.
 6. Placental insufficiency.
- Adrenaline concentration shouldn't exceed 1:200000 & maximal dose shouldn't exceed 0.5 mg.
- Felypressin is usually available for dental use only.

2) Carbon dioxide (CO₂):

- **Aim:** LAs produced with carbonated salt to speed the onset of blockade.
- After injection CO₂ lowers intracellular pH which favors the formation of the ionized active form.

3) Dextrans:

Aim: prolong the duration of action as LAs form with Dextrans Macromolecules rendering LAs to be held in tissues.

4) Hyaluronidase:

Aim: help spread of LAs as it breaks down tissue barriers e.g. ophthalmic LAs.

5) Mixture of LAs:

- Mixing LAs together to obtain the advantages of both; however LAs toxicity is additive e.g. the use of $\frac{1}{2}$ the dose of each 2 drugs is of no benefit in reducing the toxicity.

► **Examples:**

1. Lignocaine + Bupivacaine: it has rapid onset (Lignocaine) & long duration (Bupivacaine).

If an ester is combined with an amide, the toxicity may increase as the amide decreases hydrolysis of the ester by inhibition of plasma cholinesterase.

2. EMLA cream (**EUTECTIC** (easily melted) **MIXTURE OF LOCAL ANESTHETIC**):

▪ **Consists of:** mixture of the base (unionized) form of Lignocaine & Prilocaine in cream formula which penetrates skin with some reliability.

▪ **Onset:** within 1 hour.

▪ **Duration:** 1-2 hours.

▪ **Dose:** 1-2 gm of cream/10 cm² area of skin.

▪ **Useful in:**

- Pediatric anesthesia.
- Skin grafting.
- Laser removal of port-wine stain.
- Lithotripsy.

▪ **Side effects:** skin blanching, erythema and edema.

▪ Contraindications:

- On mucus membranes or broken skin as there will be more absorption and increased risk of met-hemoglobinemia (Prilocaine)
- Pts with predisposition to met-hemoglobinemia.

6) Analgesic drugs:

▶ **Aim:** to increase duration and intensity of block.

▶ **Examples:**

- Opioids (Morphine, Pethidine, Fentanyl).
- Ketorolac.
- Ketamine (0.5 mg/kg)
- Neostigmine.
- Clonidine (75-150 mg for epidural)

7) Others:

- Na hydroxide and HCL: to adjust pH.
- Na chloride: to adjust tonicity.
- Glucose and H₂O: to adjust baricity (Heavy Marcaine is Bupivacaine + 8% glucose).
- NaHCO₃: to speed up onset.

Other drugs used in anesthesia

INCLUDE:

- ▶ Cholinesterase inhibitors.
- ▶ Anti-cholinergics.
- ▶ Adrenergic agonists.
- ▶ NSAIDs.
- ▶ Metoclopramide.
- ▶ H₂-blockers.

CHOLINESTERASE INHIBITORS

Mechanism of Action:

- ▶ Reversal of N-M blockade depends on gradual diffusion, redistribution, metabolism, and excretion from the body of the nondepolarizing relaxant (**spontaneous reversal**) or on the administration of specific reversal agents (**pharmacological reversal**).
- ▶ Cholinesterase inhibitors indirectly increase the amount of acetylcholine available to compete with the nondepolarizing agent, thereby reestablishing normal neuromuscular transmission.
- ▶ Cholinesterase inhibitors inactivate acetylcholinesterase by reversibly or irreversibly binding to the enzyme. The stability of the bond affects the duration of action:
 - The bonding of **Edrophonium** is short-lived.
 - The bonds of **Neostigmine** and **Pyridostigmine** are longer lasting.
 - **Organophosphorus compounds** form very stable irreversible bonds to the enzyme.

General Pharmacological Characteristics:

Cholinesterase inhibitors leads to both Nicotinic and Muscarinic effects, so they can act at cholinergic receptors of several other organ systems, including the following:

- ▶ **CVS receptors:** Muscarinic stimulation results in vagal-like bradycardia that can progress to sinus arrest.
- ▶ **Pulmonary receptors:** Muscarinic stimulation can result in bronchospasm (smooth muscle contraction) and increased respiratory tract secretions.
- ▶ **Cerebral receptors:** Physostigmine crosses BBB and can cause diffuse activation of the EEG by stimulating muscarinic and nicotinic receptors within CNS.
- ▶ **GIT receptors:** Muscarinic stimulation increases peristaltic activity (esophageal, gastric, and intestinal) and glandular secretions (e.g. salivary, parietal).
Perioperative bowel anastomotic leakage, nausea and vomiting, and fecal incontinence have been attributed to the use of cholinesterase inhibitors.
- ▶ **Urinary system:** Muscarinic stimulation results in increased urinary bladder tone.
- ▶ **Eye:** Muscarinic stimulation results in pupillary constriction.

Unwanted muscarinic side effects are minimized by prior or concomitant administration of anticholinergics as Atropine or Glycopyrrrolate.

Specific Pharmacological Characteristics:

	Neostigmine	Pyridostigmine	Edrophonium	Physostigmine
Chemically	Quaternary amine with carbamate group	Incorporated quaternary amine with carbamate group	Quaternary amine without carbamate group	tertiary amine with carbamate group
Lipid solubility & BBB crossing	Not lipid soluble & doesn't cross BBB Due to it's chemical structure	Not lipid soluble & doesn't cross BBB Due to it's chemical structure	Not lipid soluble & doesn't cross BBB Due to it's chemical structure	Lipid soluble & crosses BBB Due to it's chemical structure

	Neostigmine	Pyridostigmine	Edrophonium	Physostigmine
Onset	5-10 min	10-15 min	1-2 min	
Duration	More than 1 hour	More than 2 hours	Shortest duration of action	
Dose	0.04-0.08 mg/kg	0.1-0.4 mg/kg	0.5-1 mg/kg	0.01-0.03 mg/kg
Recommended Anti-cholinergic	Glycopyrrolate It's dose/mg of cholinesterase inhibitor 0.2 mg	Glycopyrrolate It's dose/mg of cholinesterase inhibitor 0.05 mg	Atropine It's dose/mg of cholinesterase inhibitor 0.014 mg	
REMARKS	▪ If reversal is not complete in 10 min after 0.08 mg/kg, the time for full recovery of neuromuscular function will depend on the nondepolarizing agent used and the intensity of blockade. ▪ Neostigmine is also used in: - Myasthenia gravis - UB atony - Paralytic ileus. - Neostigmine (50–100 µg) has been used as an adjunct to intrathecal anesthesia causing a prolongation of sensory and motor blockade, by inhibition of breakdown of spinal cord acetylcholine. However, side effects include nausea, vomiting, fecal incontinence, delayed recovery room discharge, and atropine-resistant bradycardia at higher doses (200 µg).		▪ Low doses should not be used, because longer-acting muscle relaxants may outlast the effects of Edrophonium while higher doses prolong the duration of action to more than 1 h. ▪ Patients at the extremes of age are not more sensitive to Edrophonium reversal (unlike the case with Neostigmine). ▪ Edrophonium may not be as effective as Neostigmine at reversing intense neuromuscular blockade, but may be more effective in reversing a Mivacurium blockade	▪ The lipid solubility and CNS penetration of Physostigmine limit its usefulness as a reversal agent for nondepolarizing blockade, but make it effective in the treatment of central anticholinergic toxicity caused by overdoses of atropine or scopolamine. ▪ It reverses some of the CNS depression and delirium associated with use of Benzodiazepines and volatile anesthetics. ▪ Physostigmine (0.04 mg/kg) has been shown to be effective in preventing postoperative shivering. ▪ Other possible muscarinic side effects include excessive salivation, vomiting, and convulsions.

ANTI-CHOLINERGICS

Classification:

- I. Natural belladonna alkaloids: which include Atropine and Hyoscine (Scopolamine).
- II. Synthetic derivatives e.g. Glycopyrrolate

Mechanisms of Action

Anticholinergics competitively block binding of acetylcholine to its receptors and prevent receptor activation. The cellular effects of acetylcholine, which are mediated through cGMP, are inhibited. The tissue receptors vary in their sensitivity to blockade. In fact, muscarinic receptors are not homogeneous, and receptor subgroups have been identified: neuronal (M_1), cardiac (M_2), and glandular (M_3) receptors.

ATROPINE

Actions:

A) CVS:

- If given IV in small doses → initial bradycardia due to stimulation of **CIC** followed by tachycardia due to **vagal block** (increased **A-V conduction**).
- If given in large doses → tachycardia.
- **On blood vessels:** has no effect except in toxic doses → coetaneous VD → Atropine flush.

B) Respiratory:

Bronchodilatation and dryness of secretions.

C) CNS:

- Stimulates **RC** and **CIC**.
- Inhibits **vomiting center** and **basal ganglia**.
- Large doses produce **Excitation**, **hallucination** and **coma**.

D) GIT:

- **Salivary secretions** and **Gastric secretions** are decreased.
- Decreased **intestinal motility** and **peristalsis** and prolong **gastric emptying time**.
- **Lower esophageal sphincter pressure** is reduced.

E) Eye:

- **Mydriasis** (pupillary dilation).
- **Cycloplegia** (an inability to accommodate to near vision).
- Loss of **reaction to light reflex**.
- Impair **drainage of aqueous humor**.

F) Urinary tract:

Relax wall and contract sphincters.

G) Thermoregulation:

Inhibition of sweat glands may lead to a rise in body temperature (atropine fever).

Doses:

- Administered IV or IM in a range of **0.01-0.02 mg/kg** up to the usual adult dose of **0.4-0.6 mg**.
- Larger intravenous doses up to **2 mg** may be required to completely block the cardiac vagal nerves in treating severe bradycardia.

Uses:

1. Pre-anesthetic medication to:

- Decrease salivary and bronchial secretions & prevent bronchospasm.
- Antagonize RC depressants.
- Protect heart from bradycardia induced by some general anesthetics.
- Prevent vomiting.

2. Cardiac arrest up to 3 mg → Complete Vagal block.
3. Sinus bradycardia, Heart block & Carotid sinus syndrome.
4. A derivative of atropine, Ipratropium bromide, is available in inhalers for the treatment of bronchospasm.
5. To measure errors of refraction in uncooperative pts and also fundus examination.
6. Peptic ulcer, colics, and gut hypermotility.
7. Nocturnal enuresis and urinary urgency to reduce bladder motility.
8. Parkinsonism.
9. Hyperhidrosis.
10. Motion sickness but Hyoscine is better.
11. In cholinergic poisoning to antagonize the muscarinic effects as in organophosphorus poisoning or Physostigmine poisoning.

Side effects:

Dry mouth, blurring of vision, tachycardia, urine retention, glaucoma, flush and hyperthermia.

SCOPOLAMINE

Actions:

As Atropine +

- Scopolamine is a more potent antisialagogue than Atropine and causes greater CNS effects (results in drowsiness and amnesia, although restlessness and delirium) the sedative effects may be desirable for premedication but can interfere with awakening following short procedures.
- Scopolamine prevents motion sickness.
- The lipid solubility allows transdermal absorption.
- Scopolamine is best avoided in patients with closed-angle glaucoma.

Doses:

The premedication dose of Scopolamine is the same as that of atropine, and is usually given IM.

GLYCOPYRROLATE

Physical Structure:

Glycopyrrolate is a synthetic quaternary ammonium containing mandelic acid in the place of tropic acid.

Actions:

As Atropine +

- Because of a quaternary structure, Glycopyrrolate cannot cross the BBB and is almost always devoid of CNS and ophthalmic activity.
- Potent inhibition of salivary gland and respiratory tract secretions.
- Heart rate usually increases after IV but not IM.
- Glycopyrrolate has a longer duration of action than Atropine (2-4 h versus 30 min after IV administration).

Doses

The usual dose of Glycopyrrolate is $\frac{1}{2}$ that of Atropine. The premedication dose is 0.005-0.01 mg/kg up to 0.2-0.3 mg in adults.

ADRENERGIC AGONISTS

Classification:

I. Catecholamines:

- A. Natural: Adrenaline, Noradrenalin and Dopamine.
- B. Synthetic: Dobutamine, Isoprenaline.

II. Non-catecholamines: as Ephedrine, Amphetamine.

Mechanism of action:

- ▶ Direct action on adrenergic receptors as Catecholamines.
- ▶ Indirect action through release of Noradrenalin as Ephedrine, Amphetamine.
- ▶ Mixed action (Dual mechanism) as Ephedrine.

ADRENALINE

Actions: (α and β stimulant) See General pharmacology

Dose:

- In emergency situations (e.g., shock and allergic reactions), Adrenaline is administered as an IV bolus of 0.05-1 mg depending on the severity of cardiovascular compromise.
- To improve myocardial contractility or heart rate, a continuous infusion is prepared 1 mg in 250 ml normal saline (4 $\mu\text{g/ml}$) and run at a rate of 2-20 $\mu\text{g/min}$.

Uses:

1. In Cardiac arrest during CPR.
2. Complete Heart block.
3. Allergy: Acute bronchial asthma (SC, inhalation), Angioneurotic edema and anaphylactic shock
4. With Local anesthetics.
5. Local decongestant.
6. Haemostatic as in epistaxis.
7. Open angle glaucoma to $\downarrow$ IOP.

Side effects:

1. Restlessness, Anxiety, Headache.
2. Tachycardia, angina pain and Arrhythmia.
3. Elevation of BP that may lead to cerebral hemorrhage.
4. Gangrene if used with local anesthetics in fingers or toes.
5. Repeated use produces necrosis of BV and myocardium which can be prevented by use of $\alpha+\beta$ blockers and Ca^{++} channel blockers.

Contraindications:

1. IHD.
2. Hypertension.
3. Pulmonary embolism.
4. Hyperthyroidism.
5. With Cardiac glycoside, Halothane, non selective β -blockers.
6. With local anesthetics in fingers, toes and circumcision.
7. With supersensitive receptors as with MAOI, Sympatholytics and Ganglion blockers.

NORADRENALINE

Actions: (α and β_1 stimulant) See General pharmacology.

Direct α_1 -stimulation in the absence of β_2 -activity induces intense **vasoconstriction** of **arterial** and **venous** vessels. **Increased myocardial contractility** from β_1 -effects may contribute to a rise in **ABP**, but increased afterload and reflex bradycardia prevent any elevation in cardiac output.

Decreased renal blood flow and **increased myocardial oxygen requirements** limit the usefulness of Noradrenalin to the treatment of refractory shock, which requires potent vasoconstriction to maintain tissue perfusion pressure.

Dose:

Administered as a bolus (0.1 $\mu\text{g/kg}$) or as a continuous infusion 4 mg of drug to 500 ml normal saline (8 $\mu\text{g/ml}$) at a rate of 2–20 $\mu\text{g/min}$.

Uses:

1. Acute hypotensive state:
 - Spinal anesthesia.
 - Sympathectomy.
 - Shock after proper hydration.
2. With local anesthetics.

Side effects:

1. Anxiety, Headache.
2. Bradycardia, Excessive hypertension.
3. Extravasation leads to sloughing and necrosis.
4. Gangrene if used with local anesthetics in fingers or toes.

Contraindications:

1. Hypertension.
2. With local anesthetics in fingers, toes and circumcision.
3. With supersensitive receptors as with MAOI, Sympatholytics and Ganglion blockers.

DOPAMINE

Actions & Doses: (α , β_1 , D_1 receptors stimulant which is dose dependant and also releases Noradrenalin)

	Low rate (Dopaminergic dose)	Moderate rate (Beta dose)	High rate (Alpha dose)
Dose	2-3 $\mu\text{g/kg/min}$	6-8 $\mu\text{g/kg/min}$	10-12 $\mu\text{g/mg/min}$
Receptor stimulated	Dopaminergic (D_1) receptor (in renal, Coronary, cerebral, mesenteric BV)	β_1 receptor	α receptor
Effect	VD $\rightarrow$ decreases peripheral resistance AND increases RBF & UOP.	+ve Inotropic & +ve Chronotropic $\rightarrow$ Increased COP & SBP.	Generalized VC
Blocked by	Haloperidol (D-blocker)	Propranolol (β -blocker)	Phentolamine (α -blocker)

Uses:

1. Shock (Cardiogenic, Septic & Hypovolemic) after proper hydration and correction of hypovolemia.
2. Heart failure without hypertension.

Side effects:

1. Ventricular arrhythmia and anginal pains.
2. Nausea, vomiting and headache
3. Interaction with MAOI $\rightarrow$ rise in BP.

DOBUTAMINE

Actions:

- β_1 and weak α stimulant.
- +ve Inotropic more than Chronotropic.
- Has little effect on peripheral resistance.
- Doesn't stimulate Dopaminergic receptors.

Dose:

IV infusion 2.5-10 $\mu\text{g/kg/min}$.

Uses:

1. Cardiogenic shock e.g. Myocardial infarction.
2. Heart failure without hypertension.

Side effects:

1. Ventricular arrhythmia (less than Dopamine), tachycardia and anginal pains.
2. Nausea, vomiting and headache.

EPHEDRINE

Actions: (α and β stimulant) as Adrenaline but with weaker sympathomimetic effect, delayed onset and longer duration (due to slow metabolism in the liver).

Repeated administration leads to what's called **TACHYPHYLAXIS** which is acute acquired tolerance (repeated administration of the same dose $\rightarrow$ decreased hypertensive response) which is probably due to depletion of Noradrenalin stores.

Dose:

- In adults: administered as a bolus of 2.5-10 mg.
- In children it is given as a bolus of 0.1 mg/kg.
- Subsequent doses are increased to avoid the development of tachyphylaxis.

Side effects & contraindications: as Adrenaline.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Mechanism of action:

Since prostaglandins are involved in inflammation, pain and fever so the analgesic, anti-inflammatory and anti-pyretic effects are due to the inhibition of cyclooxygenases (COX 1 & 2), which prevents the formation of inflammatory mediators such as prostaglandins and thromboxanes.

REMARK:

Types of Cyclooxygenase enzymes:

- o Cyclooxygenase enzyme 1 (COX-1): in BV, stomach & kidney.
- o Cyclooxygenase enzyme 2 (COX-2): which is induced in inflammation by cytokines and inflammatory mediators.

Side effects

► **Common:**

1. GI effects (gastritis, peptic ulcer, GI bleeding, abdominal pain, nausea, vomiting, and diarrhea).
2. Decreased hemostasis (platelet dysfunction), surgical bleeding.
3. Renal dysfunction and failure.
4. Drug interactions (displace other drugs from binding sites in plasma ptns e.g. oral hypoglycemic and warfarin).

► **Other effects:**

1. Hepatic necrosis.
2. Asthma, vasomotor rhinitis, angioneurotic edema, urticaria, laryngeal edema.
3. Hypotension, impede cartilage repair.

Contraindications:

1. History of peptic ulcer disease or intolerance to NSAIDs.
2. History of bleeding diatheses, or anticoagulant therapy;
3. Renal failure, renal dysfunction, or risk factors for renal dysfunction.
4. Viral illness in children as it may lead to Reye's syndrome.
5. During pregnancy to avoid prolonged labour, postpartum hemorrhage and intra-uterine closure of ductus arteriosus (if there is need Paracetamol is recommended).

Classification:

A) Non-selective COX inhibitors:

- Salicylates: Aspirin.
- Pyrazolone derivatives e.g. Phenylbutasone.
- Indole derivatives e.g. Indomethacin.
- Anthranilic acid derivatives e.g. Mefenamic acid.
- Propionic acid derivatives e.g. Ibuprofen, Ketoprofen.
- Aryl acetic acid derivatives e.g. Diclofenac, KETOROLAC.
- Oxicams e.g. Piroxicam (Felden), Tenoxicam (Epicotil).
- Aniline derivatives e.g. Paracetamol.

B) Selective COX-2 inhibitors: e.g. Celecoxib, Rofecoxib, Parecoxib.

Appear to have lower toxicity, in particular fewer GI side effects, and have little effect on platelet aggregation.

KETOROLAC

Potency: A standard dose of Ketorolac provides analgesia equivalent to 6–12 mg of Morphine administered by the same route.

Onset & duration: Onset is also similar to Morphine, but Ketorolac has a longer duration of action (6–8 h).

Doses:

- **Loading dose** of **60 mg IM** or **30 mg IV**.
- **Maintenance doses** of **15-30 mg** every 6 hr.
- **Maximum dose** in the 1st day is **150 mg** and **120 mg** thereafter.
- Elderly patients clear Ketorolac more slowly and should receive reduced doses.

Other Parenteral NSAIDs

- ▶ NSAIDs that have been used parenterally include Diclofenac, Ketoprofen, and Parecoxib. Whereas Ketorolac and Diclofenac are nonspecific cyclooxygenase (COX) inhibitors, Parecoxib is a selective COX-2 inhibitor.
- ▶ **Diclofenac** has been administered at a dose of **1 mg/kg IV**, whereas for **Parecoxib** the dose has been **20-40 mg IV** to adults.

METOCLOPRAMIDE (PRIMPERAN)

Mechanism of action:

- ▶ Anti-emetic action: through blocking of D₂ receptors in CTZ.
- ▶ Prokinetic action: it stimulates motility of GIT especially upper part through stimulation of release of Ach from cholinergic neurons and may sensitize the intestinal smooth muscles to Ach, but it doesn't increase GIT secretions.
- ▶ Also it modulates serotonin receptors.

Uses:

- ▶ **Anti-emetic** especially as preanesthetic medication, post-operative vomiting, cancer chemotherapy, radiation sickness and in hiccup.
- ▶ **Facilitates small bowel intubation** and **increase gastric emptying** in emergency operations to prevent aspiration of gastric content, after vagotomy or in diabetic gastroparesis and in reflux esophagitis.
- ▶ **May provide some degree of analgesia** in conditions associated with smooth muscle spasm (e.g., renal or biliary colic, uterine cramping), because of its cholinergic and dopaminergic effects. It may also reduce the analgesic requirements in patients undergoing prostaglandin induced termination of pregnancy.

Side effects:

Parkinsonism, Hyperprolactinemia, Galactorrhea and Menstrual disturbances.

Doses:

- ▶ An adult dose of 10-20 mg of Metoclopramide (0.25 mg/kg) is effective orally, IM, or IV (injected over 5 min).
- ▶ Higher doses (1-2 mg/kg) have been used to prevent emesis during chemotherapy.
- ▶ The onset of action is much more rapid following parenteral (3-5 min) than oral (30-60 min) administration.
- ▶ Because Metoclopramide is excreted in the urine, its dose should be decreased in patients with renal dysfunction.

Drug Interactions

- ▶ Antimuscarinic drugs (e.g. Atropine, Glycopyrrolate) block the GI effects of Metoclopramide.
- ▶ Metoclopramide decreases the absorption of orally administered Cimetidine.
- ▶ Concurrent use of Phenothiazines or Butyrophenones (Droperidol) increases the likelihood of extrapyramidal side effects.
- ▶ Metoclopramide decreases dosage requirements for Thiopental induction of anesthesia.
- ▶ It does not reverse the effects of low-dose Dopamine infusion on the renal vasculature.

For other anti-emetics refer to general pharmacology.

H₂-BLOCKERS

Mechanism of Action

- ▶ H₂-Receptor antagonists include **Cimetidine**, **Famotidine**, **Nizatidine**, and **Ranitidine**.
- ▶ These agents competitively inhibit histamine binding to H₂-receptors leading to:
 - Reduction of **gastric acid** output (Basal, Nocturnal, Diet stimulated, and stress or drug induced) and rise of gastric pH.
 - Reduction of **Pepsin** formation.
 - Reduction of **Intrinsic factor** secretion.
- ▶ Nizatidine is available only in an oral formulation.
- ▶ Doesn't block H₁, M, β-receptors or pancreatic secretion.

Uses:

1. Treatment of peptic duodenal and gastric ulcers.
2. Hypersecretory states (Zollinger-Ellison syndrome).
3. Gastroesophageal reflux disease (GERD).
4. IV preparations are used to prevent stress ulceration in critically ill patients.
5. By decreasing gastric fluid volume and hydrogen ion content, H₂-blockers reduce the perioperative risk of aspiration pneumonia.

REMAK:

Duodenal and gastric ulcers are usually associated with **Helicobacter pylori** infection, which is also treated with combinations of Bismuth, Tetracycline, and Metronidazole. Ranitidine bismuth citrate with Clarithromycin may also be used for peptic ulcers associated with **H pylori** infection.

Side Effects:

1. Rapid intravenous injection of Cimetidine and Ranitidine has been rarely associated with **hypotension**, **bradycardia**, **arrhythmias**, and **cardiac arrest**. These adverse cardiovascular effects are more frequent following the administration of Cimetidine to critically ill patients, while Famotidine can be safely injected IV over a 2 min period.
2. **Complications of long-term Cimetidine therapy include:**
 - Hepatotoxicity (elevated serum transaminases).
 - Interstitial nephritis (elevated serum creatinine).
 - Granulocytopenia and thrombocytopenia.
 - Cimetidine also binds to androgen receptors → gynecomastia and impotence.
 - Cimetidine has been associated with changes in mental status ranging from lethargy and hallucinations to seizures, particularly in elderly patients.
 - In contrast, **Ranitidine**, **Nizatidine**, and **Famotidine** do not affect androgen receptors and penetrate the BBB poorly.

Doses:

- ▶ **Ranitidine:**
 - Dose: 50 mg IV, 150-300 mg orally.
 - Onset: 1-2 hr.
 - Duration: 10-12 hr.
- ▶ **Famotidine:**
 - Dose: 20 mg IV, 20-40 mg orally.
 - Onset: 1-2 hr.
 - Duration: 10-12 hr.
- ▶ **Cimetidine:**
 - Dose: 300 mg IV, 300-800 mg orally.
 - Onset: 1-2 hr.
 - Duration: 4-8 hr.

Drug interactions:

- ▶ **Cimetidine** is enzyme inhibitor (cytochrome P 450) → ↓ the metabolism of many drugs as Lidocaine, Propranolol, Diazepam, Theophylline, Phenobarbital, warfarin, and Phenytoin.
- ▶ **Ranitidine** is a weak inhibitor of the cytochrome P-450 system, and no significant drug interactions have been demonstrated.
- ▶ **Famotidine** and **Nizatidine** do not appear to affect the cytochrome P-450 system.